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Cerebral Deficits IN ALCOHOLISM

Edited by D. Adrian Wilkinson

ADDICTION RESEARCH FOUNDATION

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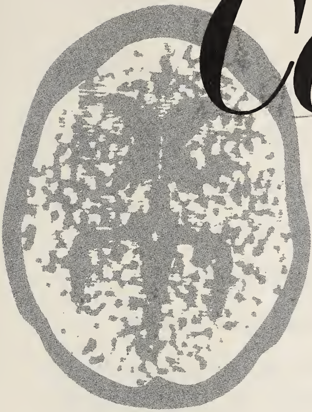

Cerebral Deficits IN ALCOHOLISM

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D. Adrian Wilkinson

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Foreword

D. Adrian Wilkinson

Five years after the symposium that resulted in the publication of "Alcohol, Drugs and Brain Damage" (1975)*, it was possible to hold a second small symposium with a similar theme. Because the second symposium was smaller than the first, and because alcohol has received more research attention than other drugs, we decided to restrict our attention to alcohol-related brain damage.

When planning the symposium we felt that there were four research currents of particular interest in the study of alcohol-related brain damage. These areas were identified as follows: (1) the etiology of alcohol-related brain damage; (2) methodological problems in the study of alcohol-related damage; (3) the prevalence of alcohol-related brain damage; and (4) recovery from alcohol-related brain damage. The participants in the symposium were invited because we knew that their current research was particularly relevant to at least one of these subjects. As the organizer of the symposium, I was exceptionally fortunate to be able to persuade all those who had been initially invited to attend the meeting. These papers are the result of that event and need little further introduction. It should be noted, however, that one of the good aspects of small conferences is that they can be organized to permit plenty of time for discussion. In our conference we had as much time for discussion of papers as we did for presentation. As a participant, I particularly enjoyed this aspect. The different discussions were led by Drs. Bill Corrigall, Kevin Fehr, John McLachlan, Mary Anne Linseman, Alan Ogborne, Constantine X. Poulos, and Harvey Skinner, all of whom deserve thanks. The editor and speakers were impressed by the quality of the discussion and its influence is, I know, felt in some of the final drafts of chapters in this volume.

One pleasing aspect of editing this work has been to see how much our knowledge in this area has increased in the short time since Rankin's volume was published. However, one can also see from the presentations that there are enormous challenges ahead. We have some clues about etiological factors and the prevalence of alcohol-related cognitive deficits, but because of the enormous methodological problems inherent in this sort of research our knowledge is still somewhat rudimentary. The competent scientist studying alcohol-related brain damage needs to be able to deal with concepts used in epidemiology, neuropsychology, neurology, electrophysiology, and neurobiology. The complexity of the subject is both daunting and fascinating.

*Rankin, James G. (Ed.), *Alcohol, Drugs and Brain Damage*, Addiction Research Foundation, Toronto, 1975.

The present volume represents an attempt not only to review some of the recent progress that has been made in this area of research, but also to offer scientists an opportunity to describe how they see research in this area developing. I thank the participants for their efforts to realise this objective, and hope that the result captures the scientific scope, the interest and the potential importance of the phenomenon under study.

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I wish to acknowledge the diligent assistance of Maria Yeung in typing of final versions of the manuscripts and in bringing coherence of style to references and citations. Louise Goldhar gave patient assistance in the proofing of galleys and indexing, and Barbara Rutledge, Donald Murray, and Lia Hatashita were most helpful in bringing this volume to press.

D.A.W.

Investigations of Brain Function in Alcoholics: A Methodological Critique

M. Sanchez-Craig and D.A. Wilkinson

Investigations of the neuropsychology of alcoholism have been principally concerned with the following problems: (1) discriminating alcoholics from nonalcoholics, (2) identifying the nature and extent of neuropsychological deficits, (3) relating functional impairment to a presumed organic cause, (4) identifying the degree to which neuropsychological deficits are reversible, and (5) identifying etiological factors. The purpose of this paper is to illustrate the variety of methodological difficulties associated with each of these problem areas by means of examples taken from the relevant literature. The difficulties encountered in areas 1 to 4 will be described briefly, since they will be expanded upon by other participants in this symposium. Problem area 5 will be discussed in more detail and will be illustrated by a set of data collected from approximately 200 skid row alcoholics. This sample was obtained from a halfway house directed by the first author.

Neuropsychological Discrimination of Heavy Alcohol Consumers from Other Groups

An important condition when members of one set (alcoholics) have to be discriminated from members of another exclusive set (nonalcoholics) is that categorization to membership of one or other set must be unambiguously made. A major difficulty in alcoholism research is that a generally accepted definition of alcoholism is not available. This difficulty is reflected in the area of neuropsychology, where a variety of criteria have been used to categorize subjects as "alcoholic." Some investigators, for example, have systematically excluded from their sample, cases with clinically evident neurological signs (e.g., primitive reflexes, ataxia, Wernicke's encephalopathy, Korsakoff psychosis), despite the fact that these patients were clearly alcoholics. In contrast, some investigators have included in their samples anyone presenting for treatment or referred for treatment because of concern over their alcohol consumption (Tarter, 1975). Although it is quite possible that nonalcoholics may have been included in samples of alleged alcoholics, since people often refer themselves or are referred for treatment because of problems arising out of episodes of acute intoxication, it

is also possible that denial by alcoholics may have excluded many appropriate subjects from study. A recent neuropsychological and neuroradiological study by Cala et al. (1978) can be used to illustrate the difficulties that may be encountered in subject selection. Although these authors described their subjects as "heavy drinkers," and the subjects regarded themselves as "heavy social drinkers," it was found that approximately 25% had evidence of memory impairment and 73% had frank impairment at clinical neurological examination. Since Cala and her colleagues found no correlation between neurological scores and morphology, but found a significant correlation between psychological scores and morphology, this raises questions about the advisability of excluding alcoholics with neurological symptoms from neuropsychological investigations as well as the appropriateness of including subjects on the basis of self-confessed alcoholism as the only criterion.

Another serious difficulty in the field of neuropsychology is that all of the extensive body of research has been conducted with hospitalized alcoholics, and with medical or psychiatric patients as comparison groups. Since most hospitalized alcoholics are self-referred to treatment, it is likely that this selection procedure may yield an unrepresentative sample of the alcoholic population. The use of hospitalized alcoholics has apparently been determined by two important problems: The problem of finding alcoholics willing to be tested, and the problem of obtaining reliable control of the interval between alcohol consumption and testing. Although the limitation of the samples studied is understandable, and raises serious questions about the extent to which the results can be generalized to the alcoholic population, a large number of studies in South America, United States, Canada, Scandinavia, Britain, Continental Europe, and Australia, have consistently replicated the finding that alcoholics show a characteristic set of neuropsychological deficits when the appropriate tests are applied (Fitzhugh et al., 1965; Ferrer et al., 1969; Brewer & Perrett, 1971; Goldstein & Shelly, 1971; Smith et al., 1973; Long & McLachlan, 1974; Clarke & Haughton, 1975; Løberg, 1977; Wilkinson & Carlen, 1977, 1978; Cala et al., 1978; Miller & Orr, 1980). An important development in recent research has been the extension of the psychological and neurological procedures to samples of social drinkers and normals by Parker and Noble (1977), and Bergman et al. (1978). Parker and Noble have demonstrated that there is a significant correlation between alcohol consumption and performance of neuropsychological tests in heavy, and in moderate or light social drinkers. The work of these authors may represent a dramatic extension of our ability to generalize the results of neuropsychological investigations to the population of drinkers at large.

Nature and Extent of Neuropsychological Deficits

In 1941, Wechsler provided a description of the kind of cognitive deficits that he believed alcoholics will typically show. This description arose from data obtained on 29 alcoholics, from his extensive clinical experience, and from his

knowledge of the psychological tests which he had developed. Wechsler stated that while some alcoholics show definite brain pathology other alcoholics do not show such pathology, but that both groups are selectively impaired on standard psychological tests. In describing the impaired abilities of the first group, Wechsler stated that: ". . . the chronic alcoholic does most poorly on tests involving organization manipulation of novel situations and relatively well on tests requiring reproduction of simple ideas or involving established habits." In describing the impaired abilities of alcoholics who were normal on clinical examination, Wechsler said that: ". . . they include not only new learning and retention, but also abstract reasoning as well as perceptual organization." It may be argued that, to a large extent, neuropsychologists have spent the past 38 years confirming the wisdom of Wechsler's clinical judgment.

The introduction in 1947 of the test battery developed by Halstead to assess what he called "biological intelligence" represented an important advancement in the area of neuropsychology. The tests in the battery are largely nonverbal and, unlike other tests of intelligence, performance is relatively unaffected by educational achievement. Halstead (1947, 1951) provided evidence in support of his belief that the tests in his battery were more sensitive than other tests in identifying brain damage, and he created an "Impairment Index." Subsequently, the battery was modified and validated by Reitan (Reitan & Davison, 1974) using a large series of neurological patients. Reitan included one of the Wechsler intelligence scales (Wechsler-Bellevue, Form 1) in the battery, and this composite psychometric assessment is now the most commonly used in the study of alcoholism. A variety of other psychological tests have been employed and consensus has arisen about certain specific deficits that alcoholics characteristically display, while other functions remain intact. Major reviews of the literature (Kleinknecht & Goldstein, 1972; Goodwin & Hill, 1975; Parsons, 1975; Tarter, 1975; Ron, 1977) report that general intelligence, verbal abilities, and memory function, are characteristically unimpaired in alcoholics without evident neurological disease. In addition, it is generally found that simple sensory and motor functions are essentially normal. Functions that have consistently been found impaired are abstraction of nonverbal concepts, conceptual shifting, and performance of complex visuospatial and visuomotor tasks. Recently, a number of investigators have demonstrated that alcoholics show deficits in the acquisition of new complex verbal material (Page & Linden, 1974; Bergman et al., 1978; Goldman et al., 1978). These data call for a reconceptualization of the pattern of impairment described in the major reviews. A move in this direction has been proposed by Goldstein (1976), who advances the following hypothesis:

> *The alcoholic maintains those kinds of abilities that would contribute to the appearance of intactness in many of the situations of everyday living, but he also has more subtle deficits in complex abilities that may provide substantial difficulties in situations in which high level adaptive functioning is required. Situations of this type often involve such capacities as planning, foresight and the*

ability to make the appropriate decision on the basis of available evidence.

The tasks on which neuropsychologists have tested alcoholics have varied in the extent to which they are verbally mediated. These tasks vary simultaneously along other dimensions, two of which can be roughly described on the following continua: *familiarity-novelty* and *simplicity-complexity.* The Picture Completion Test and the Vocabulary Test of the WAIS represent familiar tasks, whereas Raven's Progressive Matrices and Trail Making B represent much more novel activities. Similarly, Finger Oscillation is a simple task, whereas Digit Symbol substitution involves complex fine motor coordination and other functions. These dimensions of novelty-familiarity and simplicity-complexity appear to account for the ranking of the Halstead Reitan Battery and Wechsler tests on the "problem-solving stored information continuum" described by Matthews and Reitan (1963). According to Wilkinson and Carlen (1980), it appears promising to consider alcohol-related deficit as being psychological sensitivity of tasks with a high problem-solving component. A problem with most neuropsychological assessments of alcoholics is that they have typically not contained verbal tests of high problem solving difficulty nor complex visuospatial tasks low on novelty. The necessary tests of this general hypothesis (of a general problem-solving deficit in alcoholics) would require the development of test instruments involving verbal mediation combined with problem-solving, and complex visuospatial tasks that are very familiar. Verbal problem-solving might consist, for example, of anagram solution and a complex overlearned visuospatial motor task might be driving a car. The methodological issue, which can be raised from the foregoing discussion, is that descriptions of alcohol-related deficit will inevitably be limited by the range of human functions investigated.

Relationship of Functional Impairment to Morphology

An extensive literature has demonstrated that some hospitalized alcoholics show evidence of cerebral atrophy upon neuroradiological examination (cf. Parsons, 1977; Ron, 1977). *Post mortem* examinations of the brains of alcoholics have produced complementary evidence of neuropathological changes (Courville, 1955; Lynch, 1960). It is safe to conclude that some alcoholics are brain damaged. Other alcoholics show evidence of functional impairment, as described in the previous section. Several studies have now been reported in which the extent of neuroradiologically diagnosed brain pathology has been correlated with functional impairment (Ferrer et al., 1969; Brewer & Perrett, 1971; Bergman et al., 1978; Cala et al., 1978; Wilkinson & Carlen, 1978). The results of these studies have been remarkably consistent. Functional impairment on some tests is significantly related to morphological measures. However, the proportion of variance common to the two sorts of measurement is typically less than 25%. The methodological issues that can be raised from these findings concern the extent to which these low correlations reflect the inadequacy of morphological indices as measures of brain integrity and/or the inadequacy of neuropsy-

chological tests as measures of brain function (uncontaminated by the influence of subject variables such as age, education, and premorbid intelligence).

Reversibility of Neuropsychological Deficits

One might argue that the methodological flagship in the study of organic deficits in alcoholics is the investigation of reversible changes. Subjects in such studies have been randomized to conditions reflecting periods of abstinence, so that true experiments have been conducted (Page & Linden, 1974; Clarke & Haughton, 1975; Page & Schaub, 1977; Goldman et al., 1978). A remarkable feature of these experiments is the consistency of the findings. The studies have typically observed recovery of function over periods ranging from one to six months. Two important observations of these investigations have been that recovery is limited only to certain psychological functions, and that when recovery occurs it has all been accomplished in approximately the first three weeks of abstinence. Two studies by Goldman and his colleagues (Goldman & Rosenbaum, 1977) have suggested that some recovery may occur over more prolonged periods of time, but these findings have not yet been statistically confirmed, at least in the published literature*. The experimental findings are surprising in the light of clinical studies by neurologists (Victor et al., 1971; Smith, 1977; Carlen et al., 1978) who have reported that significant clinical improvement is sometimes demonstrated by abstinent alcoholics over periods of weeks and even months. Similarly, in the psychological literature, McLachlan and his colleagues (Long & McLachlan, 1974; McLachlan & Levinson, 1974) have reported significant improvements, which may have progressed slowly and were evident at one year test-retest intervals. However, the design of McLachlan's study does not preclude the possibility that the observed recovery may have occurred during the first three weeks of abstinence. An important feature of the clinical findings reported in the neurological literature is that long-term improvement is not uniformly present, but is shown by only a minority of the subjects studied. It is probable that the case material studied by neurologists may represent a much more deteriorated sample than that typically studied by psychologists, and that the apparent discrepancy between the two sets of findings may be the result of biases in subject selection.

Three methodological problems are apparent in studying reversibility of functional deficits in alcoholics. The first of these problems is not peculiar to this area of investigation and involves proper control of the sampled variable. Secondly, clinical evidence suggests that some alcoholics show remarkably little clinical improvement, whereas others show very marked improvement of extremely variable time course. If these observations are correct, they raise questions about the appropriateness of studying mean improvement in groups of alcoholics rather than using some scientifically valid case by case analysis, if such methodology can be found. The third problem that may be encountered is that

*Shortly after this paper was presented, Jenkins and Parsons (1979) reported that performance of the Wisconsin Card Sorting Test improves between the third and twelfth weeks of abstinence.

nonalcoholic groups may be used for comparison with alcoholics in an attempt to analyze the contribution of practice in performance of the test instruments. In such studies formidable problems of scaling will be encountered, if the two groups to be compared differ significantly in their initial ability on the dependent measures.

Etiological Factors

In this area of research, if reversibility studies are the flagship of methodology, then perhaps the study of etiological factors is the dredger of the fleet, where what is metaphorically dredged is historical data of questionable reliability and validity. A host of variables could be expected to contribute to brain damage and impairment of function in alcoholics, since these variables have been implicated in this manner with other groups. Most saliently these variables include head trauma, periods of unconsciousness, seizures, malnutrition, liver pathology, and consumption of drugs other than alcohol. In addition, alcohol-related variables such as duration, pattern, and level of alcohol consumption may, in themselves, contribute to brain dysfunction in alcoholics. Variables that have been empirically associated with neuropsychological functioning of alcoholics are age, years of heavy drinking, drinking pattern (episodic vs daily drinking), amount consumed per drinking occasion, time since last drink, malnutrition, liver pathology, and head injury (Jones, 1971; Jones & Parsons, 1971, 1972; Tarter & Parsons, 1971; Tarter, 1973; Page & Linden, 1974; Parsons, 1975; Page & Schaub, 1977; Parker & Noble, 1977; Goldman et al., 1978; Sanchez-Craig, 1980). However, empirical association between test performance and some of the crucial variables, e.g., age and years of heavy drinking has been inconsistently demonstrated. Effects of age and years of heavy drinking have been examined in a number of studies. Although there has been substantial variance in the classification of the two variables (e.g., "short-term" drinking has ranged on the average from approximately 3 to nineteen years), when examined independently results tend to show that it is the old and the long-term alcoholics who are mostly impaired. In studies controlling for age and education, or for age and intelligence, long-term alcoholics were found to perform significantly more poorly than short-term alcoholics in tests of visuospatial intelligence, abstracting ability, and conceptual shifting (Jones, 1971; Jones & Parsons, 1971; Tarter, 1973; Parsons, 1975). However, in studies in which both age and years of heavy drinking were simultaneously examined, a main effect of age emerged with no main effect of years of heavy drinking. A significant effect of age was found in the performance of a test of concept identification (Parsons & Prigitano, 1977) and in tests of memory, visuospatial, and visuomotor coordination (Page & Linden, 1974), but there were no significant main effects of years of heavy drinking.

Failure to control one of the variables listed above can lead to apparently contradictory findings. We intend to illustrate this point by describing a sequence of analyses, each of which can be favorably compared to those found in the literature, and several of which yielded apparently contradictory findings from the

TABLE 1: Characteristics of Male and Female Alcoholic Subjects

Subject Variables	MEN $\bar{X}$	MEN SD	WOMEN $\bar{X}$	WOMEN SD
Age (Years)*	41.9	9.4	38.6	9.6
Formal Education (Years)	9.8	2.0	9.8	2.2
Verbal Intelligence (W R V Scores)	68.8	13.7	65.7	13.7
Problem Drinking (Years)***	14.5	9.3	9.6	6.8
Abstinence before Admission to the Halfway House (Days)	27.1	25.2	24.0	26.0
Physical Consequences of Drinking (Number)	3.8	1.7	3.3	1.8

	Category	MEN %	WOMEN %
Drinking Pattern*	Daily	61.2	75.0
	Bender	37.5	22.7

* Sex difference significant at the .05 level
*** Sex difference significant at the .001 level

same data pool. The subjects of the study were 186 chronic alcoholics (120 males and 66 females) who were voluntary admissions to a halfway house for skid row alcoholics. Subjects were characterized by multiple arrests for public drunkenness: multiple entries to detoxification centres, emergency departments, and treatment services; frequent use of welfare services and skid row accommodation; impoverished social life; and poor work history. Characteristics of the subjects which are relevant to the study are presented in Table 1. The males differed significantly from the females in mean age, years of problem drinking, and drinking pattern, but not in the other listed variables.

Analysis 1

In the first analysis relevant subject variables were arranged in a correlation matrix. Variables included were those that have been found in the literature

TABLE 2: Intercorrelation between Trail Making Test Performance and Relevant Subject Variables

SUBJECT VARIABLES	Education	Verbal Intel.	Years Problem Drinking	Days Sober	Conseq. of Drinking	Trails A	Trails B
Age	0.08	0.26***	0.48***	0.13	0.02	0.28***	0.32***
Education		0.43***	0.06	0.13	0.02	0.09	0.23**
Verbal Intelligence			0.10	0.14	–0.02	–0.19*	–0.29***
Years Problem Drinking				0.04	0.34***	0.12	0.21**
Days Sober					0.00	0.09	–0.03
Physical Consequences of Drinking						0.07	0.08
Trails A							0.56***

* < .05
** < .01
*** < .001

to be related to neuropsychological functioning, and on which data were available. Sex and drinking pattern were excluded from the analysis because they are dichotomous variables. Table 2 shows the intercorrelation of the variables included. Trail Making Test performance was correlated significantly with four of the selected variables, i.e., years of education, verbal intelligence, and years of problem drinking. Days sober* and consequences of drinking** were independent of Trail Making Test performance.

*An additional ANOVA was performed on subjects tested less than two weeks after the last drink, and more than two weeks after the last drink, and no significant difference was obtained.

**Physical consequences of drinking included: blackouts, morning shakes, fits and seizures, hallucinations, numbness, and heart and stomach or liver problems. The respondants were asked to identify any of these symptoms which they or their physicians had associated with drinking.

TABLE 3: Partial Correlations between Trail Making Test Performance and Relevant Subject Variables

Subject Variables	CONTROLLED VARIABLES	TRAILS A SIG.	TRAILS B SIG.
Age	Verbal Intelligence	***	***
	Years Problem Drinking	***	***
	Verbal Intelligence + Years Problem Drinking	***	***
Education	Verbal Intelligence	NS	NS
Verbal Intelligence	Age	***	***
	Education	*	**
	Age + Education	***	***
Years Problem Drinking	Age	NS	NS
	Physical Consequences of Drinking	NS	**
	Age + Physical Consequences	NS	NS

* < .05
** < .01
*** < .001

Analysis 2

Because the four variables which were significantly correlated with Trail Making Test performance were also significantly intercorrelated, partial correlational analyses between these variables and Trail Making Test scores were conducted. The results of these analyses are presented in Table 3. As can be seen from this Table, only age and verbal intelligence remained significantly correlated with Trail Making Test performance, after partialling out the contribution of the

TABLE 4: Analyses of Trail Making Test Performance for Groups Varying in Years of Problem Drinking and Age, with Verbal Intelligence Controlled

Subject Variables	SHORT-TERM	MIDDLE-TERM	LONG-TERM
Young	X	X	
	2x2 ANOVA		
Old	X	X	X
		One-Way ANOVA	

Analysis 1: *All Ss*
  Main effect of Age from 2 x 2 ANOVA
  Main effect of Years of Problem Drinking from One-Way ANOVA
Analysis 2: *Males*
  Main effect of Age from 2 x 2 ANOVA
Analysis 3: *Females*
  Main effect of Years of Problem Drinking from One-Way ANOVA

other relevant variables. It is worth noting that verbal intelligence is apparently a more important variable to control than years of education, which is much more commonly used in matching groups of alcoholics in neuropsychological studies. A surprising result of this analysis was the disappearance of years of problem drinking as a significant correlate of Trail Making Test performance.

Analysis 3

In order to confirm the above finding, more controlled analyses using ANOVAs with matched groups were undertaken. Analyses were conducted separately for men, women, and the combined groups, employing two levels of age, three levels of years of problem drinking, and controlling for verbal intelligence. The procedure of matching groups reduced the sample size from 186 to 137 subjects. The schema for these analyses is presented in Table 4. The significant relationships emerging from the analyses are also listed in this table. (For a detailed description see Part 1 of the Appendix.) The results give evidence of a sex difference in sensitivity to the chronic effects of alcohol, a hypothesis that has some support in the literature (Hórvath, 1975). However, examination of the characteristics of the subjects revealed that there were relatively few episodic drinkers in the young short-term groups and the longer-term women. Two further analyses were, therefore, planned. — first, to compare groups of matched male and female subjects, the second to examine the possible contribution of drinking pattern.

TABLE 5: Analysis of Trail Making Test Performance for Groups Varying in Years of Problem Drinking and Drinking Pattern*

Subject Variables	SHORT-TERM	MIDDLE-TERM	LONG-TERM
Daily			
Young	X	X	
Old	X	X	X
Bender			
Young	X	X	
Old	X	X	X

Main effects of Drinking Pattern
Main effects of Age
*Age, sex, and physical consequences of drinking were used as covariates, and verbal intelligence was controlled

Analysis 4

For the analysis on sex differences criteria were established for matching men and women on age, years of problem drinking, drinking pattern, and verbal intelligence. Thirty-five pairs of subjects were obtained by this procedure. The mean Trail Making Test scores were compared using *t* tests for correlated samples, and no significant differences were obtained. (See Part II of the Appendix for a detailed description of this analysis.)

Analysis 5

Since no sex differences were found on Trail Making Test performance, men and women were included in an analysis in which the effects of drinking pattern were examined. In this analysis, two levels of drinking pattern, (bender vs daily drinking) and three levels of years of problem drinking (short-, middle-, and long-term) were included. Age, sex, and physical consequences of drinking were used as covariates. The schema of this analysis is presented in Table 5. Results showed a main effect of age and a main effect of drinking pattern. There was no significant effect of years of problem drinking. A refinement of Analyses 4 and 5 has been presented elsewhere (Sanchez-Craig, 1980).

Discussion

Methodological points highlighted by the results of this sequence of analyses are as follows: (1) Failure to examine men and women separately could have resulted in the conclusion that years of problem drinking made a significant contribution to Trail Making Test performance. (In a sense it did, but only because drinking pattern was nested in that variable, and this point would not likely be recognized by most readers.) (2) Failure to conduct a matched comparison of men and women with drinking pattern controlled, could have led to the conclusion that there was a sex difference in Trail Making Test performance. (3) Drinking pattern proved to have a main effect on Trail Making Test performance. However, this does not imply that drinking pattern *per se* causes neuropsychological deficit. Other consumption measures such as amount consumed per drinking occasion may be nested in that variable. (4) Nonarbitrary procedures can be used to select variables that are included in the studies. In the present analysis, for example, years of education and number of days sober before testing were dropped only when it was found that these variables were not significantly related to Trail Making Test performance. (5) The present study was possible because a relatively large and heterogeneous subject pool was available.

A number of factors which are common in alcoholics has been shown to affect their performance on a variety of measures of functioning. As new variables are identified, the demand for control of each variable requires that the size of the subject pool from which appropriate and adequate samples can be drawn be substantially increased. This feature of the research may imply that certain current research practices will yield diminishing returns, since single investigators may be less and less able to collect for themselves the data they need. A more productive research system would be to standardize the assessment of potential subjects and allow investigators to sample from this pool. Such a procedure would depend upon consensus among the users of the pool about assessment information that should be collected, and about the instruments that should be used to accomplish this task. At a minimum, reliable information must clearly be collected on medical status, pattern, quantity, and duration of consumption of alcohol and other drugs, and duration of abstinence before testing. Furthermore, consensus would have to be reached concerning the appropriate biological and psychological tests to be employed.

Another research strategy which may have less and less utility is the selection of carefully matched groups of subjects to test etiological hypotheses. The same ends may be achieved, at lower cost, by using multivariate analyses of the data generated from large heterogeneous samples. An increasing tendency to use this approach is evident in the recent literature (e.g., Shelly & Goldstein, 1976; Eckardt et al., 1978; Miller & Orr, 1980; Wilkinson & Carlen, 1978).

Experimental tests of some etiological hypotheses are possible if animal models of alcoholism are used. This model has obvious utility in examining the effects of alcohol on tissue, and in demonstrating that functional deficits are pro-

duced. However, the usefulness of the approach in testing hypotheses concerning the nature of functional deficits and in estimating hazardous levels of consumption in humans is very questionable. An alternative method which has not been attempted is the longitudinal study of human subjects, perhaps best accomplished by selecting from populations known to be at risk (e.g., the offspring of alcoholics). Implementation of this method is exceedingly complex, costly, and most probably unattractive to investigators and to public organizations because guaranteed financial commitment to such projects is almost never undertaken.

In summary, an overwhelming body of evidence now exists which indicates, despite the methodological problems inherent in this research, that brain damage and psychological dysfunction are associated with alcoholism and quite probably produced by the neurotoxic effects of alcohol or its metabolites. The problems that now confront the investigators are to identify the precise nature of the etiological mechanisms, of the dysfunction produced, and of the prevalence and reversibility of these effects. Unfortunately, the methodological problems in answering these questions are even more complex than those which obstructed the demonstration of the phenomenon of impairment.

APPENDIX

Part I

Effects of Age and Years of Problem Drinking

Five groups of men (N = 90) and five groups of women (N = 47) were formed for the purpose of analysis. In all the groups, verbal intelligence was statistically controlled to be close to the median Wide Range Vocabulary score for the total sample (69.4). On age, subjects were classified as Young (39 years and under) and Old (40 years and over). On years of problem drinking subjects were classified as Short-term (1–9 years for women, 1–10 for men), Middle-term (10–16 years for women, 11–23 for men), and Long-term (17–30 years for women, 24–33 for men). The number of years used to classify men and women into the above categories differed because the length of problem drinking reported by women in the sample was significantly shorter ($t = 3.95, p < .001$). Within a gender group, the mean duration of drinking of groups described as short-term, or middle-term or long-term drinkers did not differ significantly the one from the other, and there was no overlap of duration between the Short- and Middle-, and Middle- and Long-term groups. Men and women in the Young groups and men and women in the Old groups did not differ significantly in age.

Since one cell of the 2 x 3 matrix was empty of scores the data were analyzed in two steps. First, 2 x 2 ANOVAs were conducted separately for men, for women, and for the combined groups. In a second step, comparisons were made by 2 x 1 ANOVAs between Old/Middle-term and Old/Long-term subjects. These analyses were also conducted separately for men, for women, and for the com-

TABLE A: Mean Performance Times (in secs) and Standard Deviations of Trail Making A and Number of Alcoholics for Group (N) Categorized According to Age and Years of Problem Drinking, with Verbal Intelligence Statistically Controlled

Subject Variables	SHORT-TERM ($\bar{X}_{Men}$ = 6.7) ($\bar{X}_{Women}$ = 5.2)	MIDDLE-TERM ($\bar{X}_{Men}$ = 16.5) ($\bar{X}_{Women}$ = 12.7)	LONG-TERM ($\bar{X}_{Men}$ = 28.5) ($\bar{X}_{Women}$ = 23.0)
		ALL SUBJECTS	
Young ($\bar{X}$ = 33.4)	44.1 ± 26.1 (30)	37.8 ± 10.9 (29)	
Old ($\bar{X}$ = 47.8)	49.6 ± 17.7 (29)	49.3 ± 24.5 (30)	49.5 ± 16.5 (19)
		MEN	
Young ($\bar{X}$ = 34.1)	42.5 ± 26.0 (20)	36.3 ± 10.3 (19)	
Old ($\bar{X}$ = 48.0)	51.7 ± 19.4 (19)	49.1 ± 23.4 (20)	48.5 ± 17.1 (12)
		WOMEN	
Young ($\bar{X}$ = 32.7)	47.4 ± 25.0 (10)	40.7 ± 12.0 (10)	
Old ($\bar{X}$ = 47.6)	45.6 ± 13.0 (10)	49.8 ± 27.8 (10)	52.9 ± 18.1 (7)

bined groups. The means on Trail Making Test performance and the number of men and women in each group are presented in Tables A and B. Results of the 2 x 2 ANOVAs indicated a significant main effect of age on Trail Making Test performance for men (F_{TMA} = 6.01, d.f. = 1,75; F_{TMB} = 6.04, d.f. = 1,75, p = .02) and for the combined groups (F_{TMA} = 5.50, d.f. = 1,115, p = .03; F_{TMA} = 5.60, d.f. = 1,115, p = .02). The effect of age on the performance of the test by women was not significant, and the effect of years of problem drinking was not significant for any of the groups.

TABLE B: Mean Performance Times (in secs) and Standard Deviations of Trail Making B, and Number of Alcoholics per Group (N) Categorized According to Age and Years of Problem Drinking, with Verbal Intelligence Statistically Controlled

Subject Variables	SHORT-TERM ($\bar{X}_{Men}$ = 6.7) ($\bar{X}_{Women}$ = 5.2)	MIDDLE-TERM ($\bar{X}_{Men}$ = 16.5) ($\bar{X}_{Women}$ = 12.7)	LONG-TERM ($\bar{X}_{Men}$ = 28.5) ($\bar{X}_{Women}$ = 23.0)
		ALL SUBJECTS	
Young ($\bar{X}$ = 33.4)	109.4 ± 39.5 (30)	93.8 ± 38.0 (29)	
Old ($\bar{X}$ = 47.8)	130.4 ± 65.0 (29)	117.3 ± 54.9 (30)	157.1 ± 77.2 (19)
		MEN	
Young ($\bar{X}$ = 34.1)	110.1 ± 44.3 (20)	93.9 ± 37.9 (19)	
Old ($\bar{X}$ = 48.0)	138.4 ± 74.1 (19)	127.4 ± 57.3 (20)	142.0 ± 64.3 (12)
		WOMEN	
Young ($\bar{X}$ = 32.7)	108.1 ± 29.8 (10)	93.7 ± 40.2 (10)	
Old ($\bar{X}$ = 47.6)	115.3 ± 42.3 (10)	97.1 ± 45.5 (10)	182.9 ± 95.2 (7)

Results of the 2 x 1 ANOVAs between Old/Middle-term and Old/Long-term subjects showed only a significant effect of years of problem drinking on Trails B for women (F = 6.20, d.f. = 1,15, p = .03) and for the combined groups (F = 4.16, d.f. = 1,47, p = .05). No significant effect of years of problem drinking on any of the Trails was found for the groups of males.

A comparison between the results of the ANOVAs and those of the partial correlational analyses indicated: (a) that the significant contribution of age to Trail Making Test performance, when the effects of verbal intelligence were partialled out, was corroborated by the ANOVAs only with respect to men and the

combined groups (age did not contribute significantly to the performance of women); and (b) that the nonsignificant contribution of years of problem drinking to Trails B, when the effects of verbal intelligence were partialled out, was not corroborated by the ANOVAs with respect to Long-term women and the combined Long-term groups.

Part II

Sex Differences

Given that men and women in the sample differed significantly in relevant variables such as age, years of problem drinking, and drinking pattern, a matched subject analysis was conducted to test for sex differences in Trail Making Test performance. For the total sample, 35 women and 35 men were matched on drinking pattern (daily or bender). In addition, they were matched on age, years of problem-drinking, and verbal intelligence, according to the following criteria: Five units or less in either direction for age and years of problem-drinking, and 10 units or less in either direction for verbal intelligence. From the matching, 25 pairs of daily and 10 pairs of bender drinkers were obtained. Results of *t* tests for correlated samples indicated that men and women in either group did not differ significantly in their performance, $t_{TMA}(9) = 0.51$ and $t_{TMB}(9) = 0.58$ for the Bender group; $t_{TMA}(24) = 0.51$ and $t_{TMB}(24) = 0.17$ for the Daily group.

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Towards an Epidemiology of Cognitive Deficits among Alcohol Consumers

Elizabeth S. Parker and Douglas A. Parker

Almost 2,400 years ago, Hippocrates, in *On Airs, Waters, and Places*, stated that the proper investigation of medicine should include consideration of whether people are "fond of drinking." Yet today, epidemiologic investigations often fail to consider the role of alcohol consumption in the development of diseases. The general neglect of alcohol as a risk factor is true even for studies on the epidemiology of cognitive impairments despite abundant evidence that chronic alcoholics have an increased prevalence of neuropsychological deficits and brain atrophy (Parsons, 1977).

In this chapter, we present a rationale for a broadly-based examination of alcohol consumption as a risk factor in cognitive impairments. Recent findings are reviewed which indicate that social drinking as well as alcoholism may interfere with sober cognitive performance. It is proposed that research on the neuropsychological concomitants of alcoholism be expanded to consider the range of drinking practices found in the general population. Specification of the precise intake-effect relation between alcohol consumption and cognitive impairments will facilitate the development of scientifically-based recommendations about safe and harmful limits of alcohol use. In addition, knowledge about the epidemiology of alcohol-related cognitive impairments will be relevant for understanding the pathogenesis of alcoholic brain damage.

Background

Most of what we know about alcohol-related cognitive deficits involves either changes accompanying acute intoxication or impairments in sober alcoholic patients. Both psychopharmacological and neuropsychological studies

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leave little doubt that alcohol is associated with profound disruption of cognitive functions (for reviews, see Ryback, 1971; Kleinknecht & Goldstein, 1972; Grant & Mohns, 1975; Tarter, 1975; Birnbaum & Parker, 1977; Parsons, 1977). In psychopharmacologically-oriented research, the interest is in how the ability to process, organize, and remember information is altered when alcohol is in the bloodstream. Certain aspects of cognition have been found to be particularly vulnerable to disruption during intoxication. Acutely, alcohol impedes the formation of new memories (Jones, 1973; Wickelgren, 1975; Parker et al., 1976; Miller et al., 1978), the ability to monitor information coming from more than one source (Moskowitz & DePry, 1968; Moskowitz & Sharma, 1974), higher order abstraction processes (Parker et al., 1974), and some types of problem-solving (Carpenter et al., 1961; Carpenter & Ross, 1965). Regardless of whether a person is an alcoholic, a heavy drinker, or a moderate drinker, the ingestion of acute doses of alcohol can seriously disrupt cognitive performance (Parker et al., 1974; Rosen & Lee, 1976).

Whereas, psychopharmacological research delineates cognitive changes during intoxication, neuropsychological research explores the nature of cognitive deficits in sober alcoholic patients. An extreme form of intellectual deterioration associated with alcoholism is the amnesic disorder of Korsakoff's Syndrome, which is chronic and debilitating (Talland, 1965). Many alcoholic patients, who do not present with clinically diagnosible amnesic syndrome, display significant neuropsychological deficits. Alcoholics appear to have specific deficits in visual-spatial abstracting abilities, concept formation and shifting, and perceptual-motor performance (Kleinknecht & Goldstein, 1972; Goodwin & Hill, 1975; Grant & Mohns, 1975; Tarter, 1975; Parsons, 1977). Cognitive impairments in alcoholics may reflect deteriorated brain structure. Autopsy data (Courville, 1955), pneumoencephalography (Brewer & Perrett, 1971; Horvath, 1975), and more recently, some CT Scan studies (Fox et al., 1976; Epstein et al., 1977; Wilkinson & Carlen, 1977; Carlen et al., 1978; Cala et al., 1978) have found evidence of increased cerebral atrophy in alcoholics. An estimated 50% to 70% of unselected samples of alcoholics in treatment may have cortical or subcortical atrophy according to some reports (Parsons, 1977). However, as Hill cautions, such estimates often beg the question as to what constitutes abnormal degree of atrophy (this volume).

At the present time, we know very little about the neuropsychological concomitants of subalcoholismic (social) drinking although recent studies, which will be described in detail later, have found a significant association between alcohol intake and sober cognitive decrements in social drinkers. Studies of alcoholic individuals do not provide information on the full spectrum of relationships between alcohol consumption and cognitive impairments. The lack of precise quantitative information on the effects of alcohol consumption is not unique to studies of cognitive impairments but reflects a general deficiency in research on the health consequences of drinking (Turner et al., 1977, Parts A & B). In an extensive review of alcohol-related effects on various organ systems,

Turner et al. (1977) state: "All that can be concluded with confidence is that excessive alcohol intake often leads to dire results, but there is no agreement on the definition of 'excessive use' in quantitative terms" (p. 236).

Why Study Cognitive Functions in Social Drinkers?

Research on the associations between the full range of drinking patterns and cognitive performance will enhance our understanding of the etiology of neuropsychological deficits in alcoholic persons. Alcoholic brain damage may be the result of factors other than alcohol-induced damage to the central nervous system. Factors often associated with alcoholism which could produce neuropsychological deficits include malnutrition, liver disease, head trauma, and abuse of other drugs (Victor & Adams, 1961; Goodwin & Hill, 1975). For example, with regard to the pathogenesis of alcoholic dementias, Victor & Banker (1978) stated that "the role of alcohol is a secondary one, the adverse effects on the nervous system being the result of nutritional deficiency, liver disease, or both, which are engendered by chronic abuse of alcohol" (p. 149). A recent article in the *New England Journal of Medicine* proposed fortifying alcoholic beverages with thiamine as a means of preventing Wernicke's encephalopathy and Korsakoff's Syndrome (Centerwall & Cricki, 1978).

While nutritional deficiencies are linked to some types of demented states occurring in alcoholics, there is considerable evidence suggesting neurotoxic effects of alcohol or its metabolites (for review, see Freund, 1973). Walker and coworkers (this volume) have found that vitamin-enriched diets do not prevent learning deficits and morphological alterations of the hippocampus in animals who have chronically imbibed ethanol. It would appear that malnutrition cannot fully account for alcohol-related deficits in the central nervous system.

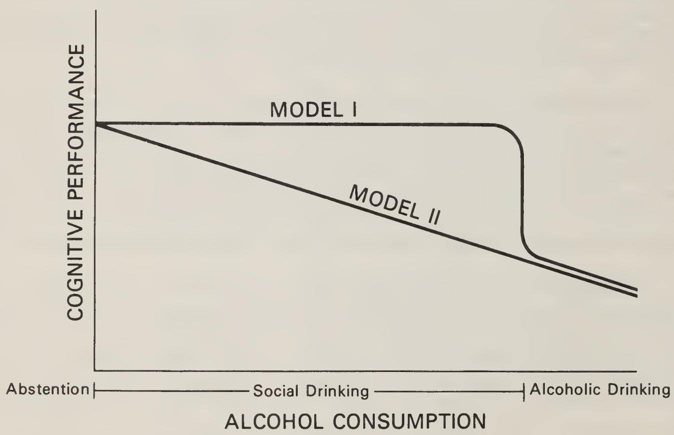
Further evidence supporting alcohol as a risk factor in cognitive impairments has been obtained in studies with alcoholic patients which have found a positive relation between drinking history and degree of deficit. In a study of alcoholic patients, Jones (1971) reported a relationship between years of alcoholism and neuropsychological deficits: long-term alcoholics (an average alcoholism history of 15 years) performed more poorly than short-term alcoholics (an average alcoholism history of three years) even though these two groups were matched for age and education. Tarter (1973) found greater cognitive deficits in subjects reporting more than 10 years of alcoholic drinking compared to those with less than 10 years of alcoholism.

Years of alcoholism is but a rough index of alcohol consumption. To take a closer look at the relation between alcohol consumption and neuropsychological deficits in alcoholics, Eckardt and coworkers measured drinking history and neuropsychological performance in 95 drug-free alcoholic patients within seven days of their last drink (Eckardt et al., 1978). Cognitive decrements were significantly correlated with both chronic and recent drinking variables when

the effects of age and education were controlled. The fact that drinking practices significantly predicted cognitive performance, whereas other variables such as history of seizures, DTs, blackouts, head traumas, or recent use of medications were not predictive of cognitive performance, supports the hypothesis that alcohol consumption plays a role in alcoholic brain damage.

Studies of alcoholic patients are extremely useful, however they are limited by a number of factors. The focus on alcoholic patients means information on the relation between alcohol consumption and cognitive impairments is based on very high levels of alcohol intake. This, as well as sampling bias inherent in clinical samples, restricts the generalizability of the results. Complimentary investigations of non-institutionalized alcohol consumers can overcome some limitations of clinically-based studies and provide more complete information on the distribution of alcohol-related cognitive decrements.

FIGURE 1



In Figure 1, two alternative models of the relation between alcohol consumption and cognitive processes are depicted. Much of the research on alcohol-related cognitive deficits assumes Model I which portrays a threshold relationship between alcohol intake and neuropsychological deficits. According to Model I, only very heavy alcohol consumption results in cognitive impairments and subalcoholismic levels of consumption are not associated with sober cognitive functioning. Alternatively, Model II depicts a continuous dose-response relation-

ship between alcohol intake and cognitive functioning such that increased alcohol consumption is associated with reduced sober cognitive performance. In Model II, a much larger proportion of the population is at risk for alcohol-related cognitive decrements than in Model I.* In both models, the greatest deficits are in the heaviest consumers. Thus, studies of alcoholic patients would not allow for the differentiation between these models. By extending research beyond samples of alcoholic patients, it becomes possible to test whether the continuous model or the threshold model best fits the data on the relation between alcohol intake and cognitive functioning. If the threshold model is better, at what level of alcohol intake does the drop in cognitive processes become evident? If the continuous model is more appropriate, what is the slope of the relation between increased alcohol consumption and decreased cognitive performance? These represent some of the key questions that require answers.

The possibility that subalcoholismic levels of alcohol consumption could interfere with the maintenance of optimum levels of cognitive functioning is not without significance for people who use alcohol in socially normative ways. In the *Third Special Report to the U.S. Congress* (Noble, 1978) it was estimated that there are between 9.3 and 10 million alcohol abusers (including alcoholics) in the total adult U.S. population or 7% of the 145 million people 18 years and older. In addition, an estimated 35% of adult Americans are abstainers, defined as a person who drinks less than once a year. Thus 58% or approximately 84 million Americans can be considered social drinkers. Social drinking is a vague term used in the present context to refer to levels of alcohol consumption below those associated with alcoholism. The term "social drinker," therefore, covers widely divergent drinking patterns. It could include a person who takes a single drink several times a year as well as someone who consumes seven or eight drinks several nights a week.

At this time, we have very little scientific data on the benefits and risks associated with various patterns of subalcoholismic levels of alcohol consumption. With regard to cognitive impairments, many social drinkers might want to know whether their use of alcohol is impeding intellectual sharpness, conceptualization processes, abstraction abilities, and memory. Our informal observations indicate that individuals whose work or identity involves intellectual skills are particularly interested in the apparent relation between social drinking and sober cognitive decrements. We have also noticed that some heavy drinkers are willing to entertain the possibility that sober cognitive decrements could result from social drinking. Nevertheless, they often point out that slight losses in cognitive capacities may not be very meaningful. Many factors, including age, can compromise brain functions so why should one be concerned about the little effect that alcohol might have? After all, was not Winston Churchill brilliant in spite of his heavy drinking?

*The present discussion of alcohol-related cognitive decrements is not restricted to levels of cognitive functioning which are considered to be in the clinically impaired range.

To illustrate the relation between cognitive decrements and social drinking, we would like to describe two people we have interviewed in research projects. Certain details are altered to protect their confidentiality, however, the essential facts remain as they were reported to us.

Example 1

Don O'Brien is a 43-year-old, top-level managerial troubleshooter for a large company. His main function is to identify and solve problems that arise in branch offices. Over the past seven years, Don has gained the reputation of being one of the best in his line of work. Not only is he extremely personable, but he has a sharp analytic mind for which he is admired.

Recently, Don has become frustrated with his working conditions. He seems to be taking longer yet is less effective in solving problems that arise. Each new problem requires that he sort through data, identify the key weaknesses, and recommend solutions. He thinks that his job is increasingly difficult because of the proliferation of government regulations, union demands and protections, and his company's expansion into new products. Don finds that he is spending too much time keeping abreast of new regulations and not enough time on the kind of work he enjoys.

At his last annual checkup, Don's physician said he was in good shape although his blood pressure was a little high. Don jogs at least three times a week and watches his diet carefully — pretty carefully. Don likes to drink and he really does not think about his drinking much. He drinks far less than his coworkers, has followed the same pattern for years, and never drinks on the job, except for business lunches. Every day, Don has a drink of scotch before dinner. If he has had a particularly tough day or is at a social gathering, he will take five to six drinks after dinner, rarely more. This might occur twice a week.

Analysis. In an average week, Don drinks every day and consumes a total of 17 drinks of scotch. Based on 1-1/2 ounces (42.6 mL) of 90-proof whiskey per drink this is roughly equivalent to an average intake of 33 g/day. Usually Don has one drink (13.7 g) and several days a week he has six drinks (82 g). Since Don is frustrated with his working conditions, he might want to know if his periodic intake of six drinks interferes with his sober cognitive processes. Very little is known about the carryover effects of this level of consumption. However, some data suggest that decreased cognitive performance is specifically related to the amount of alcohol consumed at a time (the dose of alcohol ingested on a particular occasion).

Example 2

Jacky Franklin is a bright, 39-year-old housewife-turned-student working towards a law degree at a highly competitive school. A year ago, Jacky decided she wanted "to do something meaningful with her life." Her two children were in

high school and her husband, a university professor, was moderately supportive of her desire to go back to school.

Eighteen years ago, Jacky graduated near the top of her class in political science. She knows that she is intellectually gifted and she is an extremely hard worker. Given her age and sex, Jacky believes she must do extremely well in law school if she is ever going to find a job when she graduates. Law school, however, is more difficult than she expected. She is overwhelmed by the amount of material she has to read, analyze, and remember. Although she enjoys reading the cases, she knows she has a tendency to focus on details and quite often misses the appropriate legal principles in a case. Jacky worries that her age is putting her at a disadvantage.

Jacky has always liked to drink. During the past year, she stopped drinking on week nights so she could study in the evenings. The only time she drinks now is on Saturday evening when she and her husband go out for dinner or to the home of friends. On Saturday, they have a few cocktails before dinner, split a bottle of wine with dinner, and quite often have brandy with coffee when they return home. Jacky knows she is not very sharp on Sunday but this is her day for housework.

Analysis. Jacky drinks one day a week, typically having three ounces of vodka, 14 ounces of table wine, and two ounces of brandy. This is equivalent to 100 g of alcohol once a week and an average daily consumption of 14.5 g. Her average daily consumption is low but does not reflect the intensity of consumption. Jacky gave up drinking during the week because she knew that her ability to study was impaired if she had alcohol in her system. She really never thought about the effect her Saturday evening drinking might have on her cognitive efficiency during the week.

It may be important to emphasize that research on the relation between alcohol consumption and cognitive impairments must recognize that people are going to continue to enjoy alcoholic beverages as they have for thousands of years. Yet a public health perspective encourages the collection and dissemination of scientific data on the effects of alcohol so people can make informed choices about their drinking. It is unfortunate that "normal or social drinking and levels of consumption have not come under scrutiny except by temperance movements" (Wilkinson, 1975; p. 81). Negative reactions to the temperance movement as well as prohibition have undoubtedly prevented scientific scrutiny of social drinking patterns and encouraged a focus on the health consequences of clearly deviant, very heavy alcohol abuse. However, data suggesting that social drinking could represent a health hazard often meets with vehement opposition. For example, the British medical journal *The Lancet* (1978) informed its readers about research in France indicating that alcoholic liver disease may result from lower levels of consumption than are generally considered hazardous to the liver. The studies by Pequignot et al. (1974) suggest that daily intake of 60 g in men

and 20 g in women increases the risk of liver disease. In a response, Howorth (1978) rejected this report as "scientific twaddle and scaremongering" (p. 529). Howorth went on to say, "It would be wrong to make people worry about the discrete use of nature's great comforters" (p. 529). While healthy skepticism is warranted for new and controversial findings, this should not prevent rigorous scientific investigation of the "comfort-discomfort" ratio associated with alcohol consumption. Ideally, people should be able to enjoy alcohol while minimizing its deleterious effects.

Research Findings on Cognitive Functioning in Social Drinkers

I. *Parker & Noble, 1977*

Drinking-history questionnaires were mailed to a random sample of 450 men residing in a suburban California community. Of the people who returned their questionnaire, 102 men were brought to the laboratory and took a battery of neuropsychological tests on which alcoholics are impaired. The men were asked to refrain from drinking alcohol or taking any other drugs for 24 hours before their cognitive test session.

The sample was quite homogeneous so as to minimize confounding effects of social class, social stability, and nutritional status which are often found in studies on neuropsychological deficits of alcoholic patients (Kleinknecht & Goldstein, 1972; Goodwin & Hill, 1975; Tarter, 1975). Thus, all men resided in the same community. Their mean income in 1974 was \$25,450 $\pm$\$4,755. Ninety-four percent were married and living with their spouse. In general, their occupational level was high: 40% executives and major professionals, 24% managers and lesser professionals, 35% administrators and semi-professionals, and 1% skilled laborers. Their alcohol intake, summarized in Table 1, was comparable to drinking patterns reported for men of this social class in national survey data (Cahalan et al., 1969).

The cognitive tests and descriptive references are outlined below.

1. The Shipley-Hartford Institute of Living Scale (SILS) of vocabulary and abstraction abilities also provides an impairment index called the conceptual quotient (Shipley, 1940; Shipley & Burlingame, 1941; Paulson & Lin, 1970). A number of studies have found that the SILS measures deficits in alcoholics (e.g., Page & Linden, 1974; Ornstein, 1977; Coger et al., 1978; Eckardt et al., 1978).

2. The Halstead Category Test of abstraction and adaptive abilities involves a series of geometrical figures and designs about which the subject formulates hypotheses on common themes (Halstead, 1947). Alcoholic patients display impaired performance on this

TABLE 1: Summary of Research on the Relation between Alcohol Intake and Cognitive Functioning in Alcohol Consumers

REFERENCE	SAMPLE	MEAN ALCOHOL INTAKE	FINDINGS
Parker & Noble, 1977	102 males selected randomly from an upper middle class area $\overline{X}$ Age – 43 years $\overline{X}$ Education – finished college	Drinking history questionnaire Frequency of Drinking – 202 times/yr. Quantity/Time – 42 mL Daily Intake – 23 mL Lifetime Consumption – 294 L	1. Quantity/time inversely correlated with performance on: SILS Halstead Category Test Wisconsin Card Sorting Test 2. Frequency and Lifetime Consumption did not predict cognitive performance 3. Alcohol-related decrements in memory evidenced only in heavy social drinkers
Parker & Noble, 1980	same as above	same as above	1. Strong parallels between the effects of age and of drinking on abstraction and conceptual performance 2. Greater effect of alcohol consumption in older (≥ 42 years) than in younger (< 42 years) subjects
Jones & Jones, 1980	32 female volunteers $\overline{X}$ Age – 34 years $\overline{X}$ Education – 14.8 years	Drinking history questionnaire mLs/mo. mL/day Light Drinkers 50 1.7 Moderate Drinkers 320 10.7	1. Sober memory ratio scores were significantly lower in moderate than in light drinkers 2. Moderate drinkers were more affected by acute doses of alcohol than light drinkers (1 mL/kg)
Parker, Birnbaum, Boyd, & Noble 1980	45 males who had volunteered for acute alcohol study $\overline{X}$ Age – 23 years $\overline{X}$ Education – some college	Drinking history questionnaire Freqency of Drinking – 110 times/yr. Quantity/Time – 54 mL Daily Intake – 16.3 mL Lifetime Consumption – 38 L	1. Frequency and Lifetime Consumption did not predict cognitive performance 2. Quantity/Time inversely correlated with SILS performance

test (Fitzhugh et al., 1960; Fitzhugh et al., 1965; Jones & Parsons, 1972; Kleinknecht & Goldstein, 1972; Eckardt et al., 1978).

3. The Wisconsin Card Sorting Test is performed very poorly by alcoholic patients (Tarter & Parsons, 1971; Tarter, 1973; Eckardt et al., 1978). The subject sorts a deck of cards according to three concepts: color, form, and number. Upon learning one concept, the subject is shifted to another without forewarning. This test measures specific deficits in patients with lesions in the dorsolateral frontal lobes (Milner, 1963; Malmo, 1974).

4. The multi-trial free-recall test is not a standard neuropsychological test. Recall performance is severely impaired by acute doses of alcohol and semantic organization is significantly reduced in chronic alcoholics compared to matched nonalcoholic controls (Parker et al., 1974).

There was a significant relation between alcohol consumption and sober cognitive performance. Specifically, the more alcohol subjects consumed per drinking event, the poorer was their performance on the SILS, the Halstead Category Test, and the Wisconsin Card Sorting Test. Memory and learning, as measured by the free-recall test, decreased only in the subsample of heavy drinkers (defined according to the quantity-frequency-variability index of Cahalan et al. (1969)). Some of the age and education partialled correlations between sober cognitive performance and recent drinking were quite strong: for example, 18% of the variance in general errors on the Wisconsin Card Sorting Test was accounted for by the quantity of alcohol consumed per event. In contrast to quantity of alcohol consumed per event, neither frequency of drinking nor the lifetime consumption was related to cognitive functioning.

The results of this study demonstrated an association between drinking practices and sober intellectual functioning in social drinkers. The fact that the significant drinking variable was the current quantity of alcohol consumed per drinking occasion rather than lifetime consumption, highlights the importance of current drinking practices for cognitive processes. Social drinking may not have a noticeable cumulative effect on cognitive functioning. This contrasts with the pattern in alcoholic patients in whom both chronicity of drinking as well as recent drinking practices significantly predict neuropsychological deficits (Eckardt et al., 1978).

II. *Parker & Noble, 1980*

In a further analysis of the California sample of male social drinkers, the effects of alcohol and the effects of age on intellectual processes were examined. It has been suggested that the aging brain is more sensitive to the ef-

fects of alcohol than the young brain (Jones & Parsons, 1971; Cermak & Ryback, 1976; Parsons & Prigatano, 1977) and that drinking might enhance the aging process (Courville, 1955; Kleinknecht & Goldstein, 1972; Wilkinson, this volume). Psychopharmacological studies indicate that acute doses of alcohol have a greater detrimental effect on older subjects than on younger subjects (Robertson et al., 1975; Jones & Jones, 1980). Neuropsychological studies of alcoholics have found that alcoholics show impairment on those cognitive abilities that deteriorate with age (Kish & Cheney, 1969) and that the greatest neuropsychological deficits are seen in older alcoholics (Jones & Parsons, 1971).

In the California sample, both alcohol consumption and age were associated with decreased cognitive performance. In several instances, the correlation between drinking and cognitive performance was as strong as the correlation between age and cognitive performance. For example, the simple correlation of errors in Subtest 5 of the Halstead Category Test with age was 0.33, and with amount of alcohol per event was 0.30. Although the detrimental effects of age on certain cognitive processes are well-recognized, it is somewhat surprising that nonalcoholismic drinking practices were as strongly associated with decreased cognitive performance as was age. No doubt, this pattern is specific to the present sample.

Memory appears to be much more sensitive to aging than to drinking, whereas visual spatial abstraction abilities and conceptual processes are related to both alcohol consumption and age. Perseverative errors on the Wisconsin Card Sorting Test, an index of proactive interference or the inability to inhibit a previously correct response while encoding new information, increased with age ($r = .36$) but not with alcohol consumption. Furthermore, the memory score from the free-recall task was significantly associated with age ($r = -.32$) and only with increased drinking in the subsample of heavy drinkers. Memory difficulties are not a prominent feature of the cognitive deficits in alcoholic patients (Parsons & Prigatano, 1977) unless they are intoxicated (Goodwin et al., 1972; Parker et al., 1974; Rosen & Lee, 1976). Taken together, these results indicate that abstraction and conceptual abilities are more sensitive to alcohol intake than disorders of mnemonic functioning.

By dividing the sample of 102 men at the median age of 42, the group of younger men ($\leqslant 42$ years) was compared with the older men (>42 years) to see if there was a greater effect of drinking on cognitive performance with age. The slope of the regression of Wisconsin performance on drinking was significantly steeper in the older than in the younger subsample. This supports the hypothesis that conceptual processes become increasingly vulnerable to disruption by alcohol with age. Thus, not only should research on alcohol-related cognitive deficits pay close attention to age, but also

epidemiologic studies on age-related cognitive impairments should include consideration of alcohol consumption.

III. *Jones & Jones, 1980*

Monthly alcohol intake was assessed in a sample of females who volunteered for a study on the acute effects of alcohol on memory. Subjects were asked about the quantity of beer, wine, and liquor they had consumed during the past month. Light drinkers consumed an average of 50 mL absolute alcohol over the past month and moderate drinkers an average of 300 mL. Each subject was first tested sober on a verbal memory task and then after 0.52 g of 95% alcohol/kg body weight. The memory task involved listening to lists of 12 words which were recalled both immediately and after a period of delay (short-term memory).

Light and moderate drinkers did not differ on age, education, or IQ. Moderate drinkers were significantly poorer than light drinkers in the memory ratio score which is an index of the short-term retention of words that subjects had recalled immediately. The acute dose of alcohol dramatically decreased memory performance and moderate drinkers were significantly more affected than light drinkers.

The study by Jones and Jones (1980), is the first report of alcohol-related decrements in sober cognitive performance in female social drinkers. These women were lighter alcohol consumers than the male social drinkers that have been studied; nevertheless, their use of alcohol significantly differentiated sober mnemonic functioning. This raises an important question about whether women are more sensitive to the effects of social drinking on cognitive processes than men. Interestingly, there is evidence to suggest that women are more likely than men to develop alcohol-related liver damage (Wilkinson et al., 1969; Pequignot et al., 1974).

IV. *Parker, Birnbaum, Boyd, & Noble, 1980*

Drinking history and cognitive performance were examined in 45 male university students between the ages of 21 and 30 years. Subjects completed the same drinking history questionnaire that was used in the earlier study of older male social drinkers (Parker & Noble, 1977). While sober, they completed the SILS which, as described above, has been found to be sensitive to alcohol-related cognitive decrements.

In this sample, subjects drank on the average of 100 times per year and consumed 54 mL absolute alcohol per drinking event. Even though their average drinking was lighter than in the older counterparts, the same pattern of findings was exhibited. Neither frequency of drinking nor lifetime consumption was significantly related to SILS performance. As in the earlier

study, the amount subjects consumed when they drank was the important variable: the more they consumed per drinking event the poorer their performance on the SILS. Alcohol consumption accounted for 20% to 27% of the variance in SILS scores.

This replication of the findings from the previous study and the extension to a younger age range indicate that the relation between social drinking and cognitive decrements cannot be dismissed lightly. None of the above studies, however, was designed to explore the mechanisms that account for the observed relationships.

The Role of Alcohol

The effects of social drinking on cognitive processes may be due to a carryover effect of acute intoxication. According to this model, sober cognitive decrements are a product of perturbations in the central nervous system, produced by acute intoxication, which do not necessarily return to normal as soon as alcohol leaves the bloodstream. The most dramatic type of carryover effect is seen in alcoholic withdrawal, a state of hyperexcitability characterized by hallucinations, tremor, and clouding of the sensorium (Gross et al., 1975). The severe clinical symptoms of withdrawal usually subside within several days of abstinence but some disturbances such as sleep abnormalities continue long afterwards. Wagman & Allen (1975) found that slow-wave sleep was suppressed for at least three and a half weeks subsequent to drinking. Adamson & Burdick (1973) reported that mild changes in sleep persisted in alcoholics who had been abstinent one to two years.

Withdrawal in alcoholics may be the counterpart to the hangover that occurs in social drinkers (Wallgren & Barry, 1970). Most heavy drinkers have experienced the subjective discomforts that can follow overindulgence including fatigue, headache, nausea, tremor, thirst, vertigo, elevated heartrate, and sweating. What little information is available on the after-effects of drinking is illuminating. Reversal of positional alcohol nystagmus occurs as blood alcohol levels descend and continues several hours beyond the time that alcohol can be measured in the bloodstream (Goldberg, 1963; Aschan et al., 1964; see Money & Mules, 1974 for a possible explanation). Ryback and Dowd (1972) reported that Phase II of positional alcohol nystagmus persisted beyond the obvious symptoms of hangover, up to 36 hours after alcohol imbibation. Hogman et al. (1977) measured the carryover effects of .72 g/kg alcohol on readaptation time (RAT) after photo stress in healthy subjects. RAT prolongation occurred under acute alcohol effects, recovered as blood alcohol levels reached zero, followed by a new prolongation. Nine hours after initial drinking, RAT was prolonged and this was attributed to CNS effects.

The potential significance of the after-effects of acute doses of alcohol has been recognized in the field of aviation safety. There is a federal aviation regula-

tion (91.11) known as the "8-hour rule" which states that no one may act as a crewman of a civil aircraft within eight hours after the consumption of any alcoholic beverage. In an industrial safety project, Wolkenberg, et al. (1975) observed detrimental effects 18 hours after alcohol (BAC 0.065–0.175 mg/100 mL) on simulated industrial work tasks. Delayed effects included lengthened reaction time, poor motor performance, and decreased sensory-motor processes including impaired object positioning and manipulation.

The present state of knowledge about the carryover effects of alcohol is extremely limited. There is, however, enough research to suggest that this may provide a useful framework for considering alcohol-related cognitive decrements. The fact that quantity of alcohol consumed per occasion is the drinking variable significantly associated with decreased cognitive functions certainly suggests that the level of intoxication that people reach may be important. This is further indicated by the findings that neither frequency of consumption nor lifetime consumption predicts cognitive performance in social drinkers. According to this carryover model, cognitive decrements in social drinkers are dynamically related to recent drinking. It would suggest that sober cognitive performance would increase as a function of time since last drink, and decrease as a function of amount consumed at last drinking event. Laboratory studies that measure cognitive performance at various intervals after acute intoxication would be informative.

The statistical association between alcohol consumption and cognitive decrements does not prove that drinking is a causal factor. Similarly, the finding of neuropsychological and brain morphological abnormalities in alcoholic patients does not prove that alcohol or its metabolites are directly involved. The finding that cognitive functioning in alcoholics improves with abstinence adds support to the hypothesis that alcohol consumption is a risk factor. A number of studies report neuropsychological improvement in alcoholics after varying periods of abstinence (Smith & Layden, 1971; Weingartner et al., 1971; Long & McLachlan, 1974; McLachlan & Levinson, 1974; Page & Linden, 1974; Goldman & Rosenbaum, 1977; Ornstein, 1977; Goldman, this volume). It has been reported that abnormalities in brain structure as seen in CT Scans may improve in some alcoholics with abstinence (Carlen et al., 1978; Carlen, this volume).

Research on recovery of cognitive functions has not yielded entirely consistent results. Indeed, one of the complicating factors is the confounding effect of repeated testing on the same neuropsychological tests. To examine short-term recovery, while controlling for practice effects, a battery of neuropsychological tests was administered to two randomly assigned groups of alcoholic patients (Eckardt et al., 1979). Members of one group (N = 91) were tested within seven days of their last drink and again 17 days later. Members of another group (N = 32) were tested only once, 23 days after their last drink. The repeated test group had significantly better performance on the second test administration than on the first test administration. However, when early post-withdrawal per-

formance of this group was compared to the control group who took the test battery only once after a 23-day period of abstinence, there was little evidence of recovery. Some recovery might have occurred by the first test administration and further recovery may take considerably longer than three weeks from last drink. Both practice effects and time frame must be considered carefully when attempting to examine reversibility of alcohol-related cognitive deficits (Goldman, this volume).

The role of alcohol consumption in cognitive decrements with social drinkers could be examined by assessing the effects of increased and reduced drinking practices on cognitive capacities. If social drinkers, who reduced the amount of alcohol they consumed per drinking event, exhibited significantly better cognitive performance than those who maintained their usual drinking practices, then one might conclude that drinking was directly or indirectly related to intellectual competence. It is not unreasonable to expect that reversibility occurs in social drinkers, since recent rather than past drinking practices are related to sober cognitive decrements. If the brain were not highly resilient to alcohol's depressant effects, a cumulative effect of social drinking would be apparent.

Another explanation of cognitive impairments in social drinkers is that lower cognitive abilities predisposed individuals to drink more alcohol per occasion. The abundant evidence illustrating detrimental effects of alcohol on central nervous system functioning favors viewing alcohol consumption as leading to cognitive decrements rather than cognitive decrements leading to increased alcohol consumption. Tarter (1976) has reviewed some interesting, albeit limited, research pointing to neuropsychological deficits in some alcoholics that may have existed prior to their drinking. However, further research is clearly needed to choose among these and other alternatives.

Safe and Harmful Levels of Alcohol Consumption

As noted earlier in this paper, information on the relation between alcohol consumption and health is needed so that recommendations can be formulated about levels of consumption that increase the risk of health problems. Clearly, no single recommended level of safe alcohol consumption will be applicable to all subgroups of the population or to various organ systems. The recent findings about fetal alcohol syndrome (for review see Noble, 1978) have resulted in specific recommended levels of alcohol consumption for pregnant women. Just as recommended body weight depends on sex, height, age, and fitness so will recommended alcohol intake have to be modified to fit subgroups in the population. Depending on the health index used, quite different conclusions can be reached regarding safe limits of alcohol consumption. Given the very scant amount of data on alcohol intake-effect relations and the restricted samples of social drinkers that have been investigated, it would be premature to suggest specific levels of consumption that increase the risk of cognitive deficits.

Most information pertaining to hazardous levels of alcohol consumption involves alcoholic liver diseases. It was once believed that only extremely heavy drinking for many years was damaging to the liver (for reviews see Rankin et al., 1975; Schmidt, 1975; Lelbach, 1976; Turner et al., 1977a). Lelbach (1974) reported that alcoholics with cirrhosis confirmed by biopsy had an average daily alcohol intake of 246 g, whereas alcoholics whose livers appeared normal on histological examination consumed an average of 140 g. In their review, Turner et al. (1977a) concluded that the risk of liver damage begins with regular daily intake of 80 g–100 g. French data of Pequignot et al. (1974) suggest that daily alcohol as low as 60 g in males and 20 g in females may be harmful to liver function. This finding, in conjunction with data reviewed above on cognitive decrements in social drinkers, necessitates a more careful examination of subalcoholismic levels of consumption. In addition, Klatsky et al. (1977) found elevated blood pressure in men and women who consumed three drinks or more per day (approximately 40 g). To illustrate the importance of including different indices of health, it should be noted that moderate alcohol intake may reduce the risk of coronary heart disease (e.g. Yano et al., 1977).

One serious difficulty in the epidemiology of alcohol and health is the measurement of alcohol consumption. The emphasis has been on average daily intake, an index that can mask real and potentially significant variation in drinking patterns. Suppose we have two people, one who consumes one drink and no more every day, and another who consumes seven drinks on a single occasion per week, but drinks only once a week. Both of these people have the same average daily consumption of one drink per day, yet the acute effects produced by these two patterns are very different. Our research indicates that an intense pattern of drinking is particularly significant for cognitive functioning. Whether or not this obtains for other organ systems is a question that needs to be addressed.

Research Recommendations

The primary recommendation for epidemiologic research on alcohol-related cognitive decrements is to move studies out of the traditional laboratory and clinical settings into the general population. Epidemiology is generally defined as the study of the occurrence, distribution, and determinants of states of health in the general population. In this instance, the state of health is cognitive functioning and the primary determinant or risk factor under consideration is alcohol consumption. In view of the evidence reviewed above, that levels of consumption, well below those typically associated with alcoholism, related to decrements in cognitive processes, it is quite clear that research on samples of alcoholic patients should be expanded to include a larger range of drinking practices. Unfortunately, the samples of social drinkers that have been studied to date (see Table 1) are too select and small (Ns 34–102) to estimate the distribution and extent of alcohol-related cognitive decrements. There is a very great need to assess both cognitive functioning and drinking practices in appropriately drawn,

TABLE 2: Variables To Be Included in Survey on Cognitive Impairments in Alcohol Consumers

	RECOMMENDED MEASURES
Index of Health	
Cognitive Functioning	Shipley Institute of Living Scale or Abbreviated Wisconsin Card Sort
Primary Risk Factor	
Alcohol Consumption	Frequency of Drinking Quantity per Event Variation in Drinking Lifetime Consumption Type of Beverage Time from Last Drink
Other Factors	
Demographics	Age, Sex, Education, Social Class
Physical Health	Diet, Diseases, Head Injury, Blood Pressure
Mental Health	Depression, Life Stress
Cognitive Exercise	Cognitive Complexity of Job Leisure Time Activities
Drug History	Prescription and Recreational Drug Use

large samples which will provide the scientific foundation for generalizing to the population of alcohol consumers.

One very exciting approach that calls for a close exchange among neuropsychology, epidemiology, and sociology is to include alcohol-sensitive cognitive tests in health surveys. In addition to a test of cognitive functioning, both alcohol consumption and related risk factors would also have to be assessed. The basic information that would be needed from each respondent is outlined in Table 2. These measures could be "piggy-backed" onto surveys designed for other reasons or could be included in a study specifically designed to look at drinking practices.

It will be important to select carefully the cognitive test for incorporation into survey research. The test will have to be short in order to minimize respondent burden, easy to administer, and most importantly have a demonstrated sen-

sitivity to alcohol-related deficits based on previous studies. One of the better candidates at this time is the SILS.

A study that selects an appropriate representative sample in which respondents provide both cognitive and alcohol consumption data would allow the following questions to be addressed:

1. To what extent is alcohol consumption associated with decreased cognitive performance in the general population?

2. What specific patterns of alcohol consumption are associated with reduced levels of cognitive performance? For example, are cognitive decrements primarily related to the quantity ingested per drinking event rather than to frequency of drinking or to total alcohol consumption?

3. What groups are particularly at risk for deficits in cognitive processing related to drinking?

4. Are there variables that seem to protect individuals from alcohol-related cognitive decrements?

These questions deal primarily with the nature of the association between alcohol consumption and cognitive decrements in the general population. The type of data obtained from health survey research would allow us to test whether the relationship between social drinking and cognitive performance seen in small and select samples are applicable to the general population. If the same pattern of findings is found, in other words if alcohol consumption is associated with decreased cognitive performance, then other types of research strategies will be required to look at the mechanisms underlying the observed relationship. Let us assume, for the moment, that the results from smaller studies are replicated in population-based investigations: those individuals who consume larger doses of alcohol have lower levels of sober cognitive functioning than lighter drinkers. Other types of studies would be necessary to examine whether or not alcohol consumption plays a causal role in cognitive decrements.

As suggested above, one approach for examining further the role of alcohol consumption would be to assess the effect of changes in alcohol consumption on cognitive performance. This type of study would involve a group of social drinkers who were similar in their drinking and who would be randomly assigned to either an abstain or maintain drinking condition. If social drinkers who abstained from alcohol had significantly better cognitive performance than those who maintained their normal use of alcohol, and if the groups were not different at the outset, one could conclude that alcohol consumption contributes to sober cognitive functioning.

Another etiologically-oriented study would involve a longitudinal study of young people in which their cognitive functioning would be assessed before they started drinking and reassessed some years later when their drinking practices had been established. The hypothesis would be that youth who were equivalent in cognitive abilities before they started drinking would show cognitive differences at retest that were a function of their alcohol consumption. Those young people who became heavy social drinkers would exhibit poorer cognitive performance than those who became light drinkers. The advantage of this type of study is that it would allow examination of whether young people who have cognitive impairments are more likely to become heavy drinkers. For example, are children who have minimal brain dysfunction more likely to become heavy drinkers than cognitively normal children? The key point of this design is the cognitive assessment of young people before they start to drink alcohol and a reassessment after their drinking habits have become established.

Conclusion

Awareness about physical fitness is on the rise and it is not farfetched to consider physical fitness being extended to intellectual fitness. The close relation between these areas of life was captured in the newspaper advertisement by American University, which tried to attract new students with the challenge, "Jog Your Mind." Most of us recognize that certain kinds of mental tasks become a little more difficult with age. Perhaps intellectual exercise, as well as careful monitoring of habits that may interfere with cognitive abilities, can soften the aging process. In this regard, the use and abuse of alcohol needs to be carefully and critically examined so that patterns of alcohol consumption that interfere with the maintenance of optimum levels of cognitive functioning can be identified. The dissemination of this information to the general public will permit people to make better informed decisions about their use of alcohol (Kalant & Kalant, 1971). In addition, research on possible risks of subalcoholismic levels of alcohol consumption may have significant implications for prevention, since the focus is on the early identification of health consequences in individuals who have not been engulfed by psychological and physical dependence on alcohol.

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Establishing the Cut-Offs for Brain Dysfunction Using Neuroradiological and Neuropsychological Indices: Where Should We Draw the Line?

Shirley Y. Hill

It is well known that abuse of a variety of drugs including alcohol is associated with a number of cerebral disorders (Goodwin & Hill, 1975; Parsons & Leber, in press). In spite of the fact that in the last seven years an increased number of studies has been directed toward understanding the neurological and neuropsychological concomitants of drug and alcohol use, many questions remain unanswered concerning the true prevalence of structural and/or functional deficits. Secondly, the necessary and sufficient conditions for occurrence of these disorders is currently not well understood (Parsons, 1977).

Of critical importance to answering these questions is the choice of appropriate cut-off values both for uncovering changes in neuropsychological functioning and in structural alteration. Detection of alcohol and drug-induced impairment is clearly affected by the cut-off values chosen to represent those individuals who are impaired and those who are not. Obviously, when the cut-off value is placed too low, and a large proportion of individuals fall within the "abnormal" range, the exact prevalence of these disorders is overestimated and attempts to correlate particular conditions, e.g., drinking history, with the presence of functional impairment and/or structural change will be obscured. Additional difficulties arise when the cut-off value is placed too high so that the true prevalence is underestimated, and particular consequences of alcohol and drug use are missed.

The following review will attempt to outline some of the limitations of our present knowledge about the prevalence of cerebral disorders in association with alcoholism, based on both neuropsychological and neuroradiological investiga-

tions. While specific suggestions for establishing cut-off values are currently not possible, examination of procedures commonly used or neglected may point the way to improved methods for accurate detection.

Most of the available literature concerning alcohol and drug abuse as it relates to cerebral disorders has focused on functional deficits as measured by a variety of neuropsychological procedures, most commonly the Halstead-Reitan battery, intelligence tests, and a variety of tests which measure visuoperceptive and visuomotor abilities, conceptual shifting, and short-term memory. More recently, the Luria battery (Golden, 1978) has received increased attention and may provide yet another strategy for uncovering the complex deficits occurring in association with alcohol and drug abuse.

Before 1975, very little was known about the structural changes occurring in association with alcohol and drug abuse. The few studies that had looked at cerebral atrophy used pneumoencephalography. Because of the attendant risks for patients undergoing such a procedure, fewer subjects were available for study, usually those patients whose clinical picture suggested cerebral dysfunction. The advent of Computerized Transaxial Tomography (CT) has provided a most fortuitous opportunity to discover more about the structural changes associated with drug and alcohol abuse than was ever before possible. The CT is a non-invasive technique that can be employed in subjects who, in the past, normally would not be referred for pneumoencephalography.

Attempts to delineate the conditions under which cerebral disorders occur in conjunction with alcohol and drug abuse have major implications, not only for determining the prevalence of these problems within a given population, but also for planning prevention strategies. Among the conditions which may influence detection and/or occurrence of cerebral disorders are the demographic characteristics of the individuals studied. Review of the literature indicates that a full complement of demographic variables has been identified and the effects of these variables controlled, in only a relatively small proportion of the investigations. Demographic variables such as age, race, sex, and socioeconomic status of the individuals selected for study would appear to have particular relevance (West et al., 1977). Not only are these variables relevant to assessing how the individual performs on neuropsychological tests (motivation, intelligence, test experience), but they may also affect the relative risk of developing cerebral disorders. As one example, variations in the nutritional status of economically deprived individuals may contribute to changes in brain functioning independent of the nutritional deficiencies that result from chronic alcohol consumption.

Adequate detection of alcohol-related cerebral dysfunction is often difficult because of the presence of other psychiatric disorders that may affect the psychological and neuropsychological functioning of the individuals examined. It is well known that depressed individuals have a reduced ability to concentrate, short-term memory loss, and are occasionally incorrectly diagnosed as having

organic brain syndrome. Because alcoholism and depression often appear to overlap in the psychiatric histories of the same individual, greater attention should be paid to the psychiatric history of the individual who is tested, through use of clinical interviews that describe the diagnostic criteria used both for exclusion and inclusion of subjects.

In addition to these demographic and diagnostic variables which may affect the incidence of brain damage and its detection, the particular drinking and drug history of a given individual will also alter the likelihood that identifiable deficits will occur. Among the more obvious variables influencing outcome in association with prolonged heavy use of alcohol is the frequency of drinking, the quantity consumed, the number of years the person has consumed alcohol, the pattern of drinking, and the maximum amount of alcohol consumed during the individual's heaviest consumption period. While duration of drinking has often been noted in various neuropsychological studies, pattern, frequency, and quantity of alcohol consumed are rarely assessed. However, one recent study (Sanchez-Craig, 1980; Sanchez-Craig & Wilkinson, this volume) reports changes in neuropsychological impairment as a function of drinking patterns (daily versus intermittent).

Making the picture even more complicated is the fact that individuals who are alcoholic or have alcohol-related problems may additionally have other drug problems. A few studies have been completed which attempt to measure the effects of a variety of abused drugs (Adams et al., 1975; Grant & Mohns, 1975; Grant & Judd, 1976; Grant et al., 1976, 1978). Because alcohol and other drugs having abuse potential are commonly used in combination, these investigators chose to study correlations between frequency of use of a particular drug and the presence of brain dysfunction as measured by the Halstead-Reitan battery. Attempts to link particular drugs with certain types of cognitive function were determined, in those investigations, through use of statistical (partial correlation) rather than experimental control. The assumptions underlying the use of statistical control would appear to include hypotheses which the investigator has concerning the absence of interaction effects. However, this assumption may be unwarranted in view of the fact that joint use of alcohol and other substances appears to increase the risk of certain medical consequences. As one example, Green and Jaffe (1977) have reported an increased incidence of cardiovascular and liver disorders among persons who abuse both heroin and alcohol. It is possible that the brain may similarly be affected, that is, the interaction of multiple drug use may present greater vulnerability to cerebral disorders than would be predicted on the basis of each drug alone. For this reason, further work is needed to determine the effects of drug and alcohol use among samples of individuals selected for the absence of excessive polydrug use. This goal is possible through selection criteria which would exclude individuals who exceed a predetermined level of "other" drug abuse. Obviously, there are limitations to this method as well, in that most individuals who abuse one drug often abuse others as well. However, it has been our experience that individuals can be found who meet

Feighner* and DSM III** criteria for opioid dependence only or alcohol dependence only, though one must screen at least three times the number of subjects needed for inclusion in neuropsychological or CT assessments. Secondly, a lengthy interview covering the lifetime history of drug and alcohol use must be administered to sort out appropriate individuals for study.

Assessment of neuropsychological and neuroradiological impairment is, additionally, influenced by the selection criteria imposed implicitly or explicitly by investigators who employ clinical populations for study. For example, the presence of persistent neurological problems or abnormal EEGs have been used in various investigations as both exclusion and inclusion criteria for neuropsychological and neuroradiological studies. Horvath (1975), reporting on pneumoencephalographic changes in alcoholics, found that 100% of the cases had dilatation of the lateral ventricles and widening of the cortical sulci. All of the subjects had been selected for the presence of alcoholic dementia. Five other pneumoencephalographic studies have been reported showing that 67%–100% of alcoholics studied showed brain atrophy (Haug, 1968; Castro, 1969; Carlsson et al., 1970; Ferrer, 1970; Brewer and Perrett, 1971). All but one (Haug, 1968) of these investigations employed alcoholics who were selected for "organic" disorders, "mental deterioration," or neurological problems. Because of the selection procedure employed, it is obvious that the true prevalence of cerebral atrophy in association with alcoholism may have been grossly overestimated.

Because of the risk associated with the PEG, selection procedures would require that, for ethical reasons, only individuals with an apparent medical problem could be examined. In contrast, CT studies which employ a noninvasive technique hold promise for correcting this sampling limitation. However, two recent CT studies of chronic alcoholics have failed to take advantage of this opportunity, employing subjects who were referred for CT study because of "persistent neurological problems" (Fox et al., 1976; Epstein et al., 1977). Others (Carlen et al., 1978) have overcome this difficulty by unbiased selection of alcoholics for CT and neuropsychological assessment. The design of our study included both unbiased selection of alcoholics and opioid dependent individuals and, additionally, included a normal control group selected for absence of alcohol and other drug abuse.

One hundred and seven male subjects were given an extensive battery of neuropsychological tests, and in 42 of these subjects computerized transaxial

*The alcoholic group consisted of individuals who met Research Diagnostic Criteria (Feighner et al., 1972) for alcoholism, i.e., symptoms in three or four categories: (1) any manifestation of withdrawal; (2) inability to stop drinking; (3) legal difficulty associated with drinking; and (4) social disapproval of subject's drinking. This definition also meets criteria for the proposed Diagnostic and Statistical Manual of Mental Disorders (DSM-III).

**Individuals in the opioid-dependent group met DSM-III criteria for opioid dependence which includes evidence of: (1) use of an opioid for at least one month; (2) social complications of opioid use; (3) psychological dependence; and (4) either tolerance or withdrawal.

TABLE 1: Demographic Characteristics for Subjects Given CT Scans (Mean + S.E.)

	ALCOHOLIC	OPIOID-DEPENDENT	CONTROL
Age	33.7 ± 1.4	29.5 ± 1.3	28.9 ± 1.5
Race	86.7% Black	100.0% Black	100.0% Black
Socioeconomic Index *(Best Job)*	13.5 ± 1.6	23.6 ± 4.4	27.1 ± 5.5
Education			
Some High School	60.0%	40.0%	8.3%
H.S. Graduate or Some College	40.0%	60.0%	91.7%

tomography (CT) was obtained. The present report includes only those 42 subjects given CT scans. The subjects were exclusively either alcoholics (N = 15), opioid dependent individuals (N = 15), or controls (N = 12). Use of an extensive structured interview covering life-time history of substance abuse insured that persons in the alcoholic group had never abused or become dependent on opioids and that none in the opioid dependent group had ever abused alcohol. Similarly, it was determined that the control group consisted of individuals who had never been dependent on alcohol, opioids, barbiturates, stimulants, or hallucinogens. In addition, obtaining a life-time history of drug and alcohol abuse enabled us to select groups of abusers who were relatively homogenous with respect to both frequency and quantity of abused drugs.

Subjects were drawn from outpatient alcoholism and heroin abuse programs in the St. Louis area. The selection criteria for inclusion in the study were: a minimum education of 10th grade, 25–45 years of age, and an absence of a history of head trauma sufficient to lose consciousness. The control group was drawn from churches and social groups in the St. Louis metropolitan area. The groups were matched for demographic characteristics as closely as possible (see Table 1).

CT Scans

The CT scans were performed, with the cantho-meatal line making an angle of 20° with the plane of each "slice," using a 13 mm collimator. A total of eight images were obtained based on four scanning sequences. Normal sized lateral ventricles are usually included completely in three consecutive slices. Photographic images and computer printouts used in combination allowed determination of the first lower cut showing the lateral ventricles.

Evaluation of the CT scans consisted of measuring the area of the lateral ventricles and the area outlined by tracing the inner table of the skull in each of the four slices under consideration. In those cases in which the ventricles were entirely included in three slices, the value of the ventricular area in the fourth slice was considered to be equal to zero. The sum of the areas of the ventricles in four slices were divided by the sum of areas of the cranium, and the ratio was expressed as a percentage, or ventricle/brain (V/B) index.

This method is a modification of that used by Synek et al. (1976). However, measurements taken directly from photographic pictures have a minification factor of 3.6. Also, slight errors in the measurement on a minified image lead to larger errors in computed values. Therefore, the ventricular area was determined by tracing the perimeters of the lateral ventricles and the inner table of the brain using a transparency superimposed on the numerical hard copy printout. A hand planimeter, moved around the perimeters of the lateral ventricles and cranium that had been traced, allowed measurement of each slice. All measurements were checked twice. Using this technique, the ventricular area could be determined rather than the linear distance across the ventricles, as by Huckman et al. (1975).

Halstead-Reitan Battery

Selected subtests from the Halstead-Reitan Battery were administered. These included: the Category Test, Tactual Performance Test (TPT) Time. Localization, and Memory, as well as the Finger Oscillation Test. Differences in performance were noted both for the dominant and non-dominant hand for the TPT and the Finger Oscillation Test. In addition, intelligence quotients were determined using the Peabody Picture Vocabulary Test. This test was chosen because it requires little reading skill and correlates well with the WAIS Full Scale IQ (Tobias & Gorelick, 1961). It was assumed that because many of our subjects had less than a high school education, many would be inaccurately assessed using tests requiring reading skill.

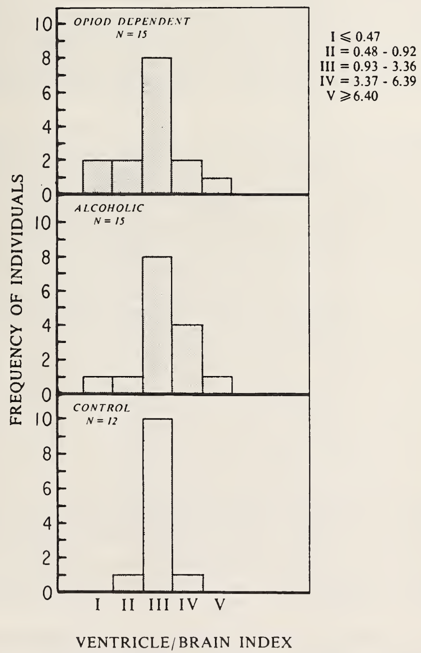
RESULTS

Computerized Transaxial Tomography

Statistical analyses of the ventricle/brain indices obtained for the three groups revealed that overall the alcoholic and opioid dependent samples did not

differ from the control sample. However, there was a tendency for both groups to differ in the proportion who were larger than the controls (alcoholic) and smaller than the controls (opioid dependent). This tendency may be seen in Figure 1 which graphically displays the distribution of V/B indices. However, statistical comparison of the alcoholics and opioid dependent individuals revealed only a trend ($X^2 = 3.40$, d.f. = 2, $p < .10$, two-tailed).

FIGURE 1



Since the presence of abnormal ventricle/brain ratios may be a threshold phenomenon, the mean and standard deviation of the entire group was calculated, and individuals who exceeded two standard deviations were classifed as

abnormal. Using this cut-off value of > 6.40, two subjects exceeded this criterion, one alcoholic with a V/B index of 8.70 and one opioid dependent individual with an index of 7.60.

Using the V/B index representing two standard deviations below the mean (0.48), two opioid dependent individuals and one alcoholic fell into this group. Due to the relatively smaller size of the CT sample, an additional measure of anatomical change, the cerebral sulci size, was determined. The size of the cerebral sulci was judged blindly by two raters and evaluated statistically. The cerebral sulci of the opioid dependent individuals were found to be significantly smaller than both the controls ($X^2 = 6.95$, d.f. = 2, $p < .01$) and the alcoholics ($X^2 = 11.47$, d.f. = 2, $p < .001$). These findings suggest that opioid dependence produces, in some individuals, neuroanatomical changes that are distinct from those seen in cerebral atrophy (enlarged ventricles and sulci), though one opioid dependent person had a V/B index suggestive of mild atrophy.

Neuropsychological test scores for our sample of 42 men given CT scans were evaluated, and comparisons made with our findings for the larger group of 107 subjects, in which detailed assessment of neuropsychological functioning was determined. In addition, a composite score, the Impairment Index, was calculated, based on the results of the following Halstead-Reitan subtests: Category, TPT (Time, Localization, and Memory), and the Finger Oscillation Test. The Impairment Index was calculated using the method of Russell et al. (1970). Results for our sub-samples of alcoholics and opioid dependent individuals (N = 42) given CT scans largely confirmed the findings obtained for the 107 subjects given neuropsychological tests, though it was not possible to obtain CT scans in the large sample. When compared with controls, both groups showed impairment on the TPT Localization and Memory, Finger Oscillation, and the overall Impairment Index (Table 2). Further, the alcoholic group showed significantly greater impairment for TPT Time (dominant and non-dominant hands), and the Impairment Index than did the opioid dependent group. Only the alcoholics showed significant deficits on the Category Test in our smaller sample though the opioid dependent group differed from the controls in the larger sample. However, in the larger sample the performance of the opioid dependent group was significantly better than the alcoholic group on the Category Test. Also, TPT (Memory) and Finger Oscillation were not found to be different in the opioid and control comparisons obtained for the larger sample.

With data available both for neuropsychological functioning and neuroanatomical changes in 42 of these men, correlation coefficients were determined between the V/B index and those test scores that reliably differed from controls, namely the Category Test, the TPT, and the overall Impairment Index. A significant positive correlation was observed for the V/B index and Category errors ($r = .27$, $p < .04$). While this correlation explains only approximately 6% of the variance, it does suggest some relationship between structural change and functional deficits.

TABLE 2: Test Scores for Subjects Given CT Scans (Mean ∓ S.E.)[1]

	ALCOHOLIC (N = 15)		OPIOID-DEPENDENT (N = 15)	CONTROL (N = 15)
Category (Errors)	72.0‡		56.6	42.3
	±7.1		±7.8	±6.9
TPT (Time)				
Dominant Hand	8.6‡	⟵ ‡ ⟶	5.2	5.5
	±0.7		±0.5	±0.4
Non-Dominant Hand	6.3	⟵ + ⟶	4.0	3.1
	±0.7		±0.4	±0.3
TPT Localization	1.9‡		2.9‡	6.6
	±0.4		±0.5	±0.4
TPT Memory	4.6‡		5.9*	7.6
	±0.5		±0.6	±0.4
Impairment Index[2]	2.3‡	⟵ + ⟶	1.6+	1.0
	±0.2		±0.2	±0.1
Finger Oscillation				
Dominant Hand	47.0+		48.3*	53.0
	±1.7		±1.4	±1.4

1 *p < .05, +p < .01, ‡ p < .001: significance calculated with respect to controls. (⟵ + ⟶) or (⟵ ‡ ⟶) indicates alcoholic group was significantly different from opioid-dependent group at .01 and .001 levels, respectively.

2 The Impairment Index was determined using the method of Russell et al. (1970). Impairment indices greater 1.55 on this scale (0 - 5.0) are suggestive of brain lesions, according to these authors.

Methodological Issues and Discussion

Overall, our CT findings do not suggest group differences in ventricular size of alcoholics when compared to a normal control group, nor are group differences apparent when an opioid-dependent group is compared with the normal controls. These findings are in apparent disagreement with the results of

Fox et al. (1976) and Epstein et al. (1977), though they generally support the findings of Carlen et al. (1978). However, the present findings may differ from the other investigations in three important ways. (1) The selection criteria employed by Fox et al. (1976) and Epstein et al. (1977) would appear to have overestimated the true prevalence of ventricular enlargement, using as they did, subjects with suspected atrophy. (2) Ventricular measurement in the Fox et al. (1976), Epstein et al. (1977), and Carlen et al. (1978) studies employed the method of Huckman (1975) for estimating ventricular size. This method differs from our own which is a modification of the Synek (1976) method which uses the perimeter of the lateral ventricles rather than the linear distances across the horns. (3) The present investigation employed a normal control group, selected for absence of drug and alcohol use and matched for demographic variables, as a standard to which we applied our results for the alcoholic and opioid-dependent groups. Using the control group data, we constructed our own cut-off value of 6.40 for the V/B index, a cut-off which is lower than that generally applied clinically (Synek, 1976, suggests 10.0). Even with the lower cut-off value, we found only one opioid-dependent individual out of 15, and one alcoholic of the total of 15, who had V/B indices exceeding this cut-off. These findings suggest that true prevalence of ventricular enlargement may be much lower than that previously reported. These findings are not meant to suggest that cerebral atrophy, as measured by ventricular enlargement, among alcoholics and drug abusers should be taken lightly, but rather suggests that certain individuals are more vulnerable to cerebral atrophy. Identification of these risk factors awaits further study. Further, these results suggest the need for large scale CT studies, if, indeed, the true prevalence in the population is low. Group differences based on small sample sizes may obscure real differences observed among a small proportion of individuals studied.

Our results for the sulci assessment were based on blind analysis of Polaroid prints as contrasted to our ventricular measurements. We chose this method realizing that the Polaroid print has a minification factor of 3.6 and the average sulcus measures only 1 mm. Attempts to measure the sulci from Polaroid prints are exceedingly difficult because boundaries are difficult to visualize and one can easily overestimate or underestimate the sulci size by 0.5 mm. Our results did, however, suggest that sulci size was enlarged among our group of 15 alcoholics. Future work will be directed toward actual measurement of sulci width using the hardcopy print-out as was done for ventricular measurement.

Finally, our neuropsychological assessments used parametric analyses of test scores rather than the proportion exceeding a predetermined cut-off score. This was possible because of the normal control group available for parametric comparison. If the effects of alcohol and drug abuse upon cerebral dysfunction represent a continuum, then parametric tests may prove to be more powerful in detecting milder forms of impairment as well as major impairment which would exceed cut-off values generally accepted by clinicians who regularly use the Halstead-Reitan Battery. We have, however, also compared our groups using

nonparametric assessment based on these cut-off values and found general agreement with our parametric analysis (Hill & Mikhael, 1979; Hill et al., 1979). For example, our alcoholics averaged 2.3 on the Impairment Index while the controls averaged 1.0. Russell et al. (1970) have suggested 1.5 as a cut-off for suspected brain damage.

In summary, our findings suggest significant neuropsychological impairment among our alcoholic and opioid-dependent groups both in terms of mean differences and the proportion of subjects exceeding generally agreed upon cut-off values. However, a much lower rate of cerebral atrophy was found using CT study. These data suggest that neuropsychological tests may be more sensitive to cerebral dysfunction than is neuroradiological assessment, or alternatively, that available cut-off scores for neuropsychological impairment may be too low. Only comparison with large samples of normal controls can answer this important question.

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Accelerated Mental Aging in Alcoholism: Working Hypothesis or Uncontrolled Variable?

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An apparent association between alcoholism and premature aging has been noted for several decades. In this paper I intend to review the variety of investigations in which this observation has been made, and to present some data which suggest that the association between age effects and alcoholism is present in the majority of alcoholics we have studied, but is not a feature of those patients exhibiting a specific memory disorder or Wernicke's encephalopathy. In conclusion, I shall speculate upon the implications of these findings for future research on alcohol-related deficits and also on the phenomenon of aging itself.

In broad terms, there is considerable agreement about the nature of the morphological, electrophysiological, and psychological concomitants of normal aging of the brain (Williams, 1970; Scheibel & Scheibel, 1975; Dustman et al., 1979).

Gross morphological changes in the brains of the aged have been reported in the literature since the observations of Esquirol (1838). He noted marked atrophy of the gyri and widening of the sulci in the brains of aged people, examined *post mortem*. These findings have since been frequently confirmed and are supported by the common clinical knowledge of neuroradiologists who observe images of living brains. Other *post mortem* observations are that the meninges are frequently thickened and somewhat opaque in older brains and tend to be adherent to the underlying brain tissue more than in younger brains (Scheibel & Scheibel, 1975). In addition, the ventricular system is often relatively dilated in old age and shrinkage of cortical grey and white matter is observed. The atrophic changes of the gyri are most marked in the frontal lobes, though not restricted to those areas only.

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Various microscopic changes are also observed in older brains. The most constant histological finding is the presence in cells of fluorescing pigments called lipochromes, or lipofuscin. The origin of these pigments is not yet definitively described, but their presence seems to be inversely related to total RNA content of affected areas of the brain, and they may have some functional significance.

Progressive loss of neurones from various brain areas seems to occur in humans from the age of about 20 onwards (Brody, 1955). In certain brain areas, the total loss may amount to 30% of the total pool. Brain areas particularly affected are the frontal and superior temporal regions of the cortex, the hippocampus, and the anterior lobes of the cerebellum. The functional significance of these changes is not understood.

The nature and total volume of the extracellular compartment also changes in the aging brain, becoming significantly reduced (Bondareff, 1973). These changes may result in reduced ability of the brain to transport small molecules and ions, thereby reducing the effectiveness of the organ.

Argyrophilic plaques or senile plaques are commonly found in hippocampus and neocortex in Alzheimer's disease, but they are also found in the brains of the non-demented aged. Neurofibrillary tangles are also common in Alzheimer's disease but are not found in the normal aging brain except occasionally in the hippocampus.

A final microscopic change that is correlated with aging has been found most marked in the prefrontal and superior temporal cortex in humans (Scheibel & Scheibel, 1975). It consists of swelling of the soma and proximal dendrites and the progressive loss of horizontally oriented dendrites. These changes may significantly affect the ability of these areas of the brain to process information.

A series of age-related electrophysiological changes in the resting and sleep EEG and in Evoked Potential (EP) responding have been noted in normal subjects. In adults, increasing age is associated with a decrease in amplitude and a decrease in frequency of the EEG alpha rhythm (Matousek et al., 1967). Evoked potential studies reveal that visual evoked potentials have larger early components, weaker late components, and longer latencies in older normal subjects (Dustman et al., 1979). Sleep EEGs also change progressively in normal subjects as a function of age (Feinberg et al., 1967; Kahn & Fisher, 1969). The elderly have increased number of arousals, more fragmented sleep patterns, short REM periods, and more stage 1 and less stage 4 sleep than younger subjects.

Psychologists attempting to create standard tests of abilities have consistently found that many abilities appear to decline steadily as a function of age. It is possible, as some have argued (Schaie, 1967), that the decline is an artifact produced by sampling error (cohort effect), but the general opinion is that some deterioration due to aging does occur, and that it may be caused by the structural

changes described above (Goldstein & Shelley, 1975). Four elements of the deterioration of psychological function with age have been described by Lezak (1976). They are: (1) deterioration of memory for events in the recent past and in the learning of new material; (2) impairment of ability for abstract reasoning and complex conceptualization; (3) inflexibility in changing set and adapting to new situations; and (4) general psychomotor slowing. In contrast, the ability to retrieve overlearned material (e.g., vocabulary) and immediate memory function seem to be relatively spared.

There is a remarkable overlap between the changes associated with aging and those observed in chronic alcoholics. Several investigators have commented upon the similarity and concluded that alcoholism may cause premature aging of the brain.

Neuropathological Studies

In a classic monograph, Courville (1955) described his findings at autopsy of the brains of alcoholics. Gross morphological changes noted were cerebral atrophy, with widening of sulci and expansion of the cerebral ventricles. The atrophic changes appeared to be most marked in the frontal areas of the brain, but were also observed in the temporal and parietal lobes. The atrophic changes showed no lateral asymmetry. The meninges were thickened and adhesive to the underlying tissue. Microscopic examination of the brains revealed marked cell loss and architectural disruption in the cortical laminae. Courville commented on the similarity of the gross morphology and histological findings in the brains of the alcoholics and in the brains of senile people. His findings were subsequently confirmed by Lynch (1960) who conducted a more controlled study, comparing the brains of alcoholics who had not been malnourished, with brains from controls matched for age and sex.

Neuroradiological Findings

Several studies, using both pneumoencephalography and computerized tomographic (CT) scans, have demonstrated that alcoholics have enlargement of cortical sulci and cerebral ventricles (e.g., Haug, 1968; Brewer & Perrett, 1971; Wilkinson & Carlen, 1977; Cala et al., 1978). The prevalence of this finding has varied enormously from study to study, probably because of marked inconsistencies in subject selection (Parsons, 1977). Though adequate estimates of the frequency and degree of significant cerebral atrophy in the brains of alcoholics is still in dispute (see papers by Hill, and Carlen, this volume) there is, nonetheless, a consistent finding in radiological studies that the gross morphology of the brains of alcoholics resembles that of significantly older non-alcoholic subjects.

Brewer and Perrett (1971) found that enlargement of sulci was most prominent in the frontal areas, with some large sulci observable in temporal and parietal regions also. In this respect their findings are consistent with the neuropathological reports.

Electrophysiological Measures

Chronic alcoholics exhibit marked sleep disturbances, with concomitant EEG changes (Johnson et al., 1970; Johnson, 1972; Lester et al., 1975). The disruptions of sleep involve unusual amounts of body movement and frequent awakening. Lester et al. measured the sleep EEGs of a group of alcoholics who had been abstinent from alcohol for at least three weeks. The data were compared to data collected from a group of non-alcoholic age-matched controls. The alcoholic group differed significantly from the non-alcoholic group and the nature of the differences was the same as the differences between the younger and the older non-alcoholic controls. These data were very similar to data collected by Johnson et al. in a sample of skid row alcoholics. They noted that the sleep disturbances measured in chronic alcoholics were remarkably similar to those observed in older non-alcoholic subjects. Lester et al. concluded that their data were consistent with the hypothesis that chronic alcoholism is associated with premature aging of the brain.

Another electrophysiological measure by which alcoholics and non-alcoholics have been discriminated is the evoked potential (EP) response. Schenkenberg et al. (1972) demonstrated that alcoholics show no asymmetry of the Visual Evoked Potential response, at certain electrode placements. In younger non-alcoholics asymmetry of this response is usually shown, but the tendency decreases as a function of chronological age. In a later study, Porjesz and Begleiter (1979) demonstrated reduced asymmetry of VEP early component amplitude in their alcoholic subjects as compared to age-matched controls. They noted that the VEP phenomena they observed in the alcoholics have also been observed in older non-alcoholic subjects.

Neuropsychological Measures

Wechsler (1941) reported on the performance of two groups of alcoholics on his Wechsler-Bellevue Test. The two groups were different in age, one group being 10 years older than the other. Potential subjects were excluded from the study if they showed clinically apparent brain dysfunction. Wechsler described a profile of subclinical deterioration in alcoholics and he noted that the pattern of test performance was suggestive of a more rapid than normal deterioration of performance of the age-sensitive tests in his battery. He suggested that alcoholism may result in premature aging of the brain. Presumably, his hypothesis was that atrophic changes of the brain lead to this deterioration, since this was the model of normal age-related intellectual decline which he advanced in his text (Wechsler, 1958).

Subsequent to Wechsler's study, a number of observers have noted the similarity between the performance of standard psychological tests by the elderly and the pattern and level of performance of the tests by alcoholics (e.g., Kleinknecht & Goldstein, 1972; Goodwin & Hill, 1975; Blusewicz et al., 1977; Schau & O'Leary, 1977; Bertera & Parsons, 1978). Many have concluded that

chronic alcoholism is associated with accelerated or premature aging of the brain.

Animal Studies

The data described so far are clinical data with all the attendant problems of such results. Experimental findings are also consistent with the notion of accelerated aging in alcoholism. Freund and Walker have been involved in a number of studies in which alcohol supplementation of diet has been shown to produce impairment of performance and neuropathological changes in rats and mice (Freund, 1970; Freund & Walker, 1971; Riley & Walker, 1978; Walker et al., this volume). It is interesting to note that the learning task selected for study in these experiments (Shuttlebox avoidance) is one on which performance deteriorates significantly in mice as they age normally. The alcoholized mice were performing as if they were prematurely aged. Furthermore, examination of the neurones from the hippocampus of such animals (Riley & Walker, 1978) revealed structural changes of the same sort as have been observed in aged rats (Feldman, 1976) and humans (Scheibel & Scheibel, 1975).

One matter that has not been discussed by the various authors who have suggested that alcoholism is associated with premature aging of the brain, is precisely what is meant by the term "premature aging." Perhaps the magical allure of the parallels between the aged and alcoholics has made people a little careless about their theories. Aging usually refers to maturational and other changes in physiology and behavior which occur in sequence through the life of the organism under study. Most organisms pass through a stage in which the changes are predominantly developmental; that is, the organism is becoming "fitter" in the evolutionary sense and, after a peak of physical and psychological aptitude, the organism deteriorates. There is immense variance in the time at which deterioration begins. The crystalline lens has the distinction of starting to die before the foetus is delivered (Gregory, 1973) whereas, in many cultures at least, wisdom is said to increase until senescence. Certainly some adaptive abilities appear to increase in humans through most of their life (Demming & Pressey, 1957). If this is true and we are to take the hypothesis of premature aging in alcoholics literally, we would predict that their performance of the sorts of tasks Demming and Pressey describe would be *improving at a faster rate than that found in the normal population.* I doubt that anyone would seriously advance such a hypothesis. It seems more plausible to assume that the hypothesis of "premature aging," if spelled out precisely, is one of the "fancies" referred to by Parsons in 1977.

Wechsler noted that mean brain mass decreases steadily in humans after the age of about 25. Mean scores on psychological tests show a similar pattern. Wechsler hypothesized that the change in brain mass was due in part to loss of neurones, and that loss of neurones produced the observed atrophic changes and the intellectual decline.

In alcoholics, cerebral atrophy has been noted. It is also found that their psychological test deficits are similar to those found in the aged. It is therefore tempting to conclude that the physiological cause of the two sorts of intellectual decline (age-related and alcohol-related) may be the same. This hypothesis about alcoholics appears to rest upon confirmation of the untested hypothesis of Wechsler concerning the cause of intellectual decline in the elderly.

A set of predictions can be generated from this hypothesis. They are: (1) psychological tests which are most age-related should be the most sensitive indicators of cognitive deficit in alcoholics; (2) the performance of psychological tests, particularly those related to age should be correlated with the amount of cerebral atrophy (measured by CT scan); (3) when psychological test performance is corrected for the normal effects of aging there should remain, in the alcoholics, a residual significant correlation of test performance with age, which will be most marked in the most age-related tests; (4) the intercorrelation of psychological test performance and measures of cerebral atrophy should be accounted for by the correlation of each of the variables with age of the subjects.

Some of these predictions have been tested in a sample of alcoholics we have examined (Wilkinson & Carlen, 1978). The tested predictions were all confirmed. The present report represents an extension of the previous analysis, to test all four predictions listed above by examining the intercorrelation of psychological test scores, CT scan scores, and ages of a large sample of chronic alcoholics.

METHOD

Subjects

The subjects of the study were 93 chronic alcoholics admitted to the Addiction Research Foundation's Clinical Institute. All subjects received CT scans and some psychological testing. Criteria for inclusion in the study were that the patient agreed to participate and reported heavy alcohol consumption (> 80 g ethanol/day) for at least 10 years. Potential subjects were excluded if any of the following conditions applied: age > 70 years., clinical evidence of active liver disease, history of head injury requiring hospitalization, extensive use of psychotropic drugs other than ethanol, and history of neurological disease not related to alcoholism. The sample consisted of 83 men and 10 women.

Test Procedures

1. CT Scans. Subjects received CT scans on an EMI head scanner. Whenever possible, the scans were administered in the third or fourth week of abstinence from alcohol; however, 33 subjects had scans done more than one month after they stopped drinking. None received the scan less than one week after drinking. Measures were made of the intercaudate width (Ventricle score,

V) and the sum of the width of the eight largest visible sulci (Sulcal score, S). The interhemispheric fissure and the sylvian fissures were included in the sulcal score when visible and of sufficient size. The scoring was conducted independently by two investigators and with satisfactory inter-rater reliability (all values $> .8$).

2. Psychological Testing. When possible, subjects received the Wechsler Adult Intelligence Scale (WAIS), the Wechsler Memory Scale (WMS), and a modified form of the Halstead-Reitan Neuropsychological Test Battery (HRB). Tests included in the HRB were: Categories, Tactual Performance, Seashore Rhythm, Speech Perception, Aphasia, Finger Oscillation, Perceptual Examination, and Trail Making Test (A and B). The Average Impairment Index was computed using the procedure of Russell et al. (1970). All subjects (93) received the WAIS, 92 received the WMS, and 83 received the HRB. In most cases, the testing was conducted between the end of the second and the end of the fourth week of abstinence. No subject was tested less than one week after drinking, and all but 16 within four weeks.

Analysis

All subjects were characterized either as Amnesic/Wernickes (A/W) or as Other Alcoholics (OA). To be included in the A/W group one or both of the following criteria had to be met: (1) WAIS Verbal IQ — WMS Memory Quotient $\geqslant 15$ (amnesia), and (2) presentation at hospital with, or confirmed history of, ophthalmoplegia (Wernicke's encephalopathy). All the remaining subjects were included in the group of Other Alcoholics.

Subtest scores on the WAIS were converted to scaled and to age-scaled subtest scores according to procedures described in the WAIS Test Manual and scores on the WMS and the HRB were raw scores. For purposes of comparison, the mean scores of the two groups were compared using t-tests for independent samples on all psychological test scores, three CT scan scores (V, S, and V + S), and subject age. The intercorrelations of the psychological test scores and the morphological scores (for each of the two groups) were computed. Partial correlations were also computed, with the contribution of subject age partialled out. Confidence levels were calculated on the basis of two-tailed comparisons.

RESULTS

The A/W group was composed of 25 subjects and the remaining 68 subjects were in the OA group. The mean age, summary psychological scores, and CT scan scores are presented in Table 1. The two groups did not differ significantly in age, Verbal IQ, Performance IQ, Full Scale IQ, Average Impairment Index, or Ventricle (V) score. As expected, the groups differed significantly in Memory Quotient, and the A/W group was also observed to have significantly larger Sulcal (S) and (V + S) scores ($t_{MQ} = 4.399$, d.f. $= 90$, $p < .001$; $t_S =$

TABLE 1: Comparison of Mean Scores on the Psychological Test Batteries, Age, and Morphological Scores of the Other Alcoholic (N = 68) and Amnesic/Wernicke (N = 25) Subjects

	OTHER ALCOHOLICS		AMNESIC/WERNICKE		
	$\overline{X}$	SD	$\overline{X}$	SD	t values
Age	46.97	± 10.71	48.56	± 7.62	0.78
VIQ	99.72	± 16.03	101.52	± 17.33	0.45
PIQ	96.28	± 14.08	90.56	± 14.50	1.67
FSIQ	98.10	± 15.12	96.52	± 16.45	0.41
Memory Quotient	98.51	± 20.24	79.68	± 17.05	4.40***
Impairment Index	1.91	± 0.87	2.32	± 0.83	1.95
Ventricle Score	17.95	± 4.35	19.12	± 3.86	1.23
Sulcal Score	29.54	± 11.01	35.90	± 6.70	3.32**
V + S Score	47.50	± 13.82	55.02	± 8.38	3.13**

** $p < .01$
*** $p < .001$

3.316, d.f. = 91, $p < .01$; t_{V+S} = 3.129, d.f. = 91, $p < .01$). These findings confirm results obtained from a smaller sample of the same subjects (Wilkinson & Carlen, 1978).

The two groups of alcoholics differed markedly in the degree of correlation of the morphological scores with chronological age. The OA group resembled non-alcoholics in that the degree of sulcal and ventricular enlargement was age-related (Wilkinson & Carlen, 1977, 1978). In contrast, the W/A group

showed no significant correlation of either index of cerebral atrophy with age (Wilkinson & Carlen, 1978).

A similar finding was made in respect of the correlation of age with psychological test performance. When correlations with WAIS scaled scores and HRB and WMS raw scores were computed, there were consistently significant correlations between age and test scores in the OA group and lower inconsistently significant correlations in the W/A group (see Table 2, columns Ia and Ib).

Age-scaled scores are corrected test scores in which the contribution of age to test performance is partialled out. The correlation of age to age-scaled scores is therefore expected to be zero. When age-corrected scores were used (the WAIS subtest scores and the Memory Quotient) the correlations of test score and age remained consistently significant in the OA group, but were reduced to very close to zero in the W/A group (Table 2, columns IIa and IIb). In respect to age-relatedness of performance, the W/A group was therefore normal, whereas the OA group showed age effects even after correction for normal age-related deterioration of performance. This finding is consistent with the hypothesis that some alcoholics show premature age effects on psychological testing.

In both groups there was a consistent correlation between the morphological score (V + S) and test performance. However, the pattern of correlations was different in the two groups. In the W/A group the highest correlations were seen with the tests of verbal skills from the HRB. In contrast, in the OA group the highest correlations were with the visuospatial tasks in the WAIS performance scales, the HRB, and the WMS (see Table 2, columns IIIa and IIIb). In this respect, the OA group showed a pattern that would be expected in alcoholics, and the W/A group was distinct, though not necessarily unexpectedly so (cf. Parsons, 1975; Butters & Cermak, 1976).

In the next stage of the analysis, the intercorrelations of scaled and raw scores with the morphological score were computed, with the contribution of age to the correlation statistically controlled. The results are presented in Table 2, columns IVa and IVb. In the OA group, no single test was significantly correlated with the morphological score, when the contribution of age was partialled out. In contrast, in the W/A group, age and morphology appeared to be operating relatively independently. For example, even when both age and brain morphology are significantly related to test performance (e.g., the Category Test), the correlation of morphology with performance is unaffected by statistically correcting for the contribution of age.

The last analysis was performed to test the hypothesis that the psychological tests that are most age-related in alcoholics should be the best predictors of brain morphology. The correlations between age and test score, and brain morphology and test score, were rank ordered and the Spearman coefficient was computed for the pairs of ranks from the 28 separate subtests in the

TABLE 2: Level of Significance of Simple Correlations between Psychological Test Performance and Scaled-Raw Scores, Age-Scaled Scores, and Brain Morphology Scores; and Partial Correlation of Psychological Test Scores with Brain Morphology Scores with Age as the Controlled Variable. Data for the Amnesic/Wernicke and Other Alcoholics Groups are presented.

	OTHER ALCOHOLICS (N = 69)				WERNICKE/AMNESIC (N = 25)			
	Ia	IIa	IIIa	IVa	Ib	IIb	IIIb	IVb
Test	AGE (Scaled Scores)	AGE (Age-Scaled Scores)	MORPHOLOGY	PARTIAL CORRELATION	AGE (Scaled Scores)	AGE (Age-Scaled Scores)	MORPHOLOGY	PARTIAL CORRELATION
Verbal Score	***	***	**				*	*
Information	**	**	*					
Comprehension	*		*				*	*
Arithmetic	***	**	**				*	*
Similarities	***	***	**					
Digit Span	***	*	**				**	*
Vocabulary	*	*					*	
Performance Score	***	**	***				*	
Digit Symbol	***	**	***					
Picture Comp.	***		**				*	*
Block Design	***	**	***					
Picture Arr.	***	**	***					
Object Ass.	***	*	***		*		**	**
Full Score	***	***	***				*	*

Information	***	–	**			–		
Orientation	***	–	*			–		
Mental Cont.	**	–				–	*	*
Memory Pass.	***	–	**					
Visual Rep.	***	–	***		*	–		
Assoc. Lng.	***	–	**		*	–	*	*
Memory Score	***	*	***				*	
Category	***	–	***		**	–	**	**
TPT – time	*	–	*		*	–		
– mem.	***	–	***			–		
– loc.	*	–	*			–		
Trail – A	**	–	*			–	**	**
– B	***	–	**			–	*	*
Perceptual Exam	***	–	**			–	*	*
Finger Tap.	***	–	*		*	–		
Rhythm	*	–	*		*	–		
Speech	*	–				–	***	***
Aphasia	**	–	**			–	***	***
Impairment Index	***	–	***		*	–	*	*
Mean value of r	.44	.29	.34	.07	.23	.04	.35	.34
SD_r	.12	.08	.09	.07	.15	.13	.17	.18

– indicates age-scaled scores not available
* $p < .05$
** $p < .01$
*** $p < .001$

WAIS, WMS, and HRB. The obtained value of rho was 0.83 ($p < .001$) in the case of the OA group. On the other hand, in the W/A group rho = –0.10.

DISCUSSION

The analyses described in the results section confirmed the predictions arising out of the hypothesis that alcoholics show cognitive impairment consistent with premature or accelerating aging of the brain, in the group called Other Alcoholics. Patients with psychometric evidence of memory dysfunction or with a history of Wernicke's encephalopathy were excluded from the OA group, and in the case of these patients, none of the analyses was consistent with the model of premature aging.

In the OA group, the types of tests on which alcoholics have frequently been found impaired (e.g., Category Test, Impairment Index, Digit Symbol, Visual Reproduction) were highly correlated with age, whereas tests on which alcoholics usually perform normally (e.g., Information, Comprehension, Vocabulary, Rhythm Test) were less significantly age-related. In addition, in this group of subjects, the tests that best discriminate alcoholics from normal subjects were also the best predictors of brain morphology. Using partial correlation, the correlation of brain morphology with performance was completely accounted for by statistical control of the variable age. However, if the test norms were used to correct for age, a significant correlation between corrected scores and age remained for all 11 tests of the WAIS, except Comprehension, and for the Memory Quotient of the WMS. This finding indicates that age-related changes in performance were observed which were significantly more rapid than those found in the normal population, also using a cross-sectional sample. The alcoholics in this group had significantly more age-related cerebral atrophy than a neurological control sample (Wilkinson & Carlen, 1977; Carlen & Wilkinson, 1979; Wilkinson & Carlen, 1979), and the degree of atrophy was related to the age-related psychological test scores.

The results from the Wernicke/Amnesic group are strikingly different. Subject age was not correlated with the morphological score in this group. Though some psychological test scores were predictably related to age, these scores were not the best predictors of morphological score in this group and normative correction for age effects reduced the mean correlation on the relevant tests from .20 (all 12 correlations in predicted direction, mean significantly greater than zero) to .04 (not significantly greater than zero). The psychological test scores of the W/A group were consistently correlated with the morphological scores, but in a pattern quite different from the OA group, and in a manner that was unaffected by statistical correction for age, using partial correlation.

These distinct patterns of results suggest that different pathogenic processes may be operating in the two groups. The absence of age-relatedness of the

morphological scores in the W/A group suggests a process which rapidly produces cerebral atrophy. Thiamine deficiency is implicated in Wernicke's encephalopathy, and may be involved in the alcohol amnesic syndrome, possibly interacting with high ethanol intake to produce the condition.

The strongly age-related atrophic and psychological changes seen in the OA group suggest that the subjects had been chronically exposed to neurotoxic conditions. Ethanol may be the neurotoxic agent in these cases. Evidence of alcohol-related cognitive deficits in middle class Californian social drinkers, who are unlikely to be malnourished or frequently head injured (see Parker, this volume) and evidence of behavioral and neuronal toxicity of chronic ethanol consumption in animal models (see Walker et al., this volume) lend credence to the hypothesis. The data from the OA group in this study are entirely consistent with the hypothesis that chronic ethanol consumption in humans produces atrophic changes in the brain which produce neuropsychological deficit. An alternative hypothesis is that some, as yet undetected, brain changes are produced by ethanol and these changes produce both cerebral atrophy and the neuropsychological deficits that accompany alcoholism. The demonstration of neuropsychological deficits in younger alcoholics, in the absence of demonstrable atrophic changes, is consistent with this hypothesis (see Hill, this volume).

And what of premature or accelerated aging in alcoholics? The data presented here suggest that this metaphor be reserved to apply to some, but not all, alcoholism-related cognitive deficits. At present, we have insufficient data about both the processes involved in normal age-related brain changes and the processes involved in alcoholism-related brain changes to make even tentative hypotheses about possible commonalities in these changes. However the parallels that have been described raise a tantalizing challenge to scientists working in both research areas. It is likely that advances in one area will yield dividends in the other, and the processes underlying the two sorts of brain deterioration within single experiments are already being investigated (Freund, 1979).

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Reversibility of Psychological Deficits in Alcoholics: The Interaction of Aging with Alcohol

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If the recent tide of behavioral research on alcoholism has suggested anything, it is that alcoholics are best studied not as a uniform group, but instead as a heterogeneous population which can be subdivided. This approach has been equally useful for the investigations of psychological deficits consequent to prolonged, excessive alcohol consumption. Subdivisions based upon a) subject characteristics present at the time that drinking ceases and b) the elapsed time span between the cessation of drinking and the point at which psychological abilities are assessed, have proved useful in this connection. For example, early reports of the global presence or absence of particular deficits are currently being re-evaluated in relation to particular subject characteristics such as age, drinking history, education, etc., and indications are that particular subject characteristics can predict both the presence and severity of deficit. Equally significant are the recent findings which indicate that many psychological deficits appearing in alcoholics immediately after they cease drinking recover over time as sobriety continues. In fact, evidence is accumulating that much recovery occurs within a remarkably short span after drinking ceases. Therefore many deficits, reported in early studies which assessed performance at only one time span after drinking ceased, may have been present at only that time and in no way reflected permanent deficits.

The following review briefly summarizes findings from early studies, and then moves on to review more recent work which has, through the use of more

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sophisticated methodology, extended our knowledge of psychological deficits attributable to chronic alcoholism. This review is not intended to be exhaustive, but rather to cover the highlights in this area. Finally, the work on recoverability of psychological functioning in alcoholics undertaken in our laboratories in recent years will be reviewed, followed by a variety of conclusions and suggestions for future work.

Intellectual Assessment of Alcohol-Related Impairments

One of the variety of approaches taken to elucidate the nature of the behavioral impairment resulting from chronic alcohol abuse has been to compare alcoholics to non-alcoholic control subjects on the various aspects of intellectual functioning measured by the Wechsler Intelligence Tests. The use of this test has been based on the expectation that neurological dysfunction will be reflected behaviorally as a deficit in some aspect of global intellectual functioning. Although some findings have been suggestive, inconsistencies among a group of studies on the Wechsler have kept conclusions limited.

A 1972 paper (Kleinknecht & Goldstein, 1972), after reviewing 12 studies, reports that the only reasonably consistent findings were that Wechsler Information and Vocabulary subtests remained unimpaired in alcoholics, while a less consistent indication of impairment was shown on the Digit Symbol and Object Assembly subtests. These authors argued that the following three areas of Wechsler Intelligence Test behavior were either not useful or of questionable utility. (1) Full scale IQ has not been shown to be adversely affected by excessive alcohol intake (Halpern, 1946; Murphy, 1953; Peters, 1956; Plumeau et al., 1960). (2) Fitzhugh et al. (1962), in an investigation of brain-damaged subjects, have shown that long-standing or diffuse nervous system impairment is *not* reflected in a decrease in Performance IQ relative to Verbal IQ. This finding, coupled with the expectation that alcohol abuse should result in long-term diffuse impairment, argues against studies that interpret verbal-performance differentials as representative of chronic alcohol abuse. (3) Except for the aforementioned observations (normal performance on Information and Vocabulary subjects, and possible impairment of Digit Symbol and Object Assembly subtests), Wechsler pattern analysis has not contributed to a consistent description of the function of chronic alcohol abusers.

Neuropsychological Assessment of Alcohol-Related Impairments

A second approach to the description of neuropsychological deficit has been to compare alcohol abusers to normals and diagnosed brain-damaged subjects on tests designed specifically for the assessment of neurological dysfunction. Alcoholics were noted to perform like brain-damaged subjects on the Halstead Categories and Trail Making Tests (Fitzhugh et al., 1965). Deficient performance has been seen on additional tests believed to reflect impaired abstraction and problem-solving abilities with both lower socioeconomic class subjects (Goldstein & Shelly, 1971) and middle to upper class subjects (Smith et al., 1973).

Alcoholics have also been found deficient on other tasks believed to reflect the impaired ability to abstract concepts and to solve problems, such as the Shipley Hartford Test and the General Aptitude Test Battery (Kish & Cheney, 1969; Smith et al., 1971). Tarter and Parsons (1971), in an effort to clarify the precise nature of the impaired abstracting ability, showed that their alcoholic sample had deficits, not in acquiring or shifting concepts, but in persisting with new solutions when old solutions were found to be incorrect: that is, they tended to show intrusive perseverative errors.

Parsons and his associates were among the first researchers to investigate the effects of subject characteristics (Jones, 1971; Jones & Parsons, 1971, 1972). They reported that short-term alcoholics are better than long-term alcoholics on the Ravens Progressive Matrices, a non-verbal intelligence test; and that both older subjects and those with longer drinking histories show greater deficits on the Halstead Categories test and a variety of sensory-motor tests. These deficits were interpreted as reflecting deficits in visual-spatial abstracting ability and visual-spatial intelligence, since an analysis of Halstead results revealed that the subtest most affected was primarily visual-spatial in character.

More recent work has considerably extended the range of subject variables which have been shown to affect neuropsychological performance. Eckardt et al. (1978) assessed alcoholics' performance on a wide range of neuropsychological tests within seven days of subjects' last drink. Through the use of multivariate techniques, they were able to show that combinations of different parameters of drinking patterns predicted test performance. Most notably, recent (within six months prior to the last drink) drinking variables predicted deficits on some tests, while chronic drinking variables predicted deficits on other tests; also, overall consumption predicted test performance, but only when it exceeded 400 lifetime gallons of alcohol consumed (derived from calculations based on alcoholics' self-report). Older alcoholics also had greater deficits. Sanchez-Craig (1980) also found age to predict alcohol-related deficits, but did not find years of problem drinking predictive. The novel contribution of this study was the observation that older daily drinkers performed significantly worse than older binge drinkers, but young binge drinkers were as impaired as young daily drinkers.

Summary and Observations — "One-Time" Assessment Studies

In general, studies which assess psychological deficits in detoxifying alcoholics with one-time testing batteries have shown that global intellectual functioning is unimpaired. In contrast, the ability to abstract and conceptualize is impaired, as is visual-spatial and simple sensory-motor performance. Deficits are more commonly found in older subjects and subjects with longer drinking histories. Lastly, recent work has indicated differences in pattern of alcohol consumption to predict deficits.

Two observations are warranted in connection with these findings of the "one-time" testing studies. (1) There are numerous methodological variations

from study to study so only tentative conclusions are justified. The problem of differences in performance within the broad grouping of "alcoholics" is only beginning to be addressed. Furthermore, recent observation of reversibility over time of some deficits (to be reviewed next) necessitates the re-examination of all one-time testing studies in that the deficits observed may be only temporary. Chronic alcoholism may be associated with many deficits in only the early phases of detoxication. (2) The efforts that have been made to relate test findings to permanent lesions in the central nervous system (CNS) may be premature in alcoholics. In fact, the results of recent studies undermine such an attempt (Wilkinson & Carlen, 1980). Test performance is based on many factors in addition to a structurally intact CNS. The observation that certain functions recover suggests that transitory mechanisms are responsible for the deficits, perhaps even actual reversibility of cerebral atrophy (Carlen et al., 1978). An additional possibility is that tasks showing the most impairment are those to which individuals in our society get the least exposure (practice). Hence differences in impairment levels among differing tasks may reflect a learning factor, rather than brain damage. Results of the above studies are consistent with such an interpretation, in that tasks which are frequently practised (verbal tasks) in our society show the least deficits. This issue will be further addressed later.

Recovery of Function Following Detoxification

With the observation that functional recovery occurs in alcoholics once they stop drinking, came the recognition that prior reports of the presence or absence of particular deficits may have reflected the particular point in the recovery cycle at which assessment was undertaken. Bennett (1960) took the lead in this work with his report of an "intermediate" stage of alcoholic brain dysfunction which appeared to recover after some months of abstinence in some alcoholics. He based his report on EEG data and psychological test findings, but then unfortunately neglected to report the psychological test results. This finding was replicated by Adamson and Burdick (1973), who did EEG sleep studies on volunteer subjects who had ceased drinking one to two years prior to the study. The only difference found between this group and normals was an elevation in the number of sleep-stage changes. To summarize a series of EEG sleep findings: early in withdrawal, sleep appears fragmented, and slow wave (stages 3 and 4) sleep is decreased; after one week following the cessation of drinking this condition subsides; and after one to two years, sleep seems to return to normal. However, these researchers point out that volunteer subjects may be self-selecting for minimal deterioration.

Since Bennett's (1960) work, studies using a variety of tests of psychological functioning have reported improvement during the period of alcohol-free time occurring after detoxification in chronic alcoholics. Before reviewing these studies, it is important to note two methodological considerations which can restrict the interpretation of psychological recovery. First, improved performance on tasks administered more than once over a limited time span may

be due to practice with the task, rather than recovery from psychological dysfunction. To preclude this interpretation, it is essential that efforts be made to control for the effects of practice.

Second, the use of only two data points on the recovery curve may prevent specification of the exact parameters of psychological recovery. Studies by Page and Linden (1974), Page and Schaub (1977), while examining a sequence of recovery points and using controls for practice effects, found improvement of a number of psychological tasks to occur within the first week and three weeks respectively following detoxification, with no further improvement thereafter. This improvement may reflect recovery from the acute stages of alcoholic dysfunction. However, some other studies have examined only two data points over a time span larger than one week. While these studies report improvement over the longer time span, all the improvement demonstrated may actually have taken place during the first week after detoxification but have gone unobserved until the second assessment point.

In the cognitive realm, improvement in short-term memory and new learning ability has been reported over a period of three weeks after detoxification, using verbal learning tasks (Allen et al., 1971a; Allen et al., 1971b; Weingartner et al., 1971), but without controls for possible practice effects. Long and McLachlan (1974), using a one-year delay period to control for practice effects, report improvement on the Wechsler-Bellevue. However, the aforementioned studies by Page and Linden (1974), and Page and Schaub (1977) found recovery over only the first few weeks following detoxification on other cognitive measures such as the WAIS and the Shipley Institute of Living Scale. Therefore, it cannot be ascertained whether results showing improvement in cognitive performance over time spans greater than one to two weeks are artifacts of the greater time delays between only two data points, or are due to actual improvement of specific cognitive functions that take longer to recover. In contrast, Page and Schaub (1977) report in a recent study that no recovery occurred beyond the first few weeks on a number of tests of intellectual functioning, even when assessment took place over as much as 25 weeks post-drinking. Clarke and Haughton (1975) report similar results after 10 weeks on two verbal and two performance subtests of the WAIS.

Similar inconsistencies in the specification of recovery parameters are present in the area of visual-motor performance. Tarter and Jones (1971) found reversibility of dysfunction over eight weeks' post-detoxification on the Purdue Pegboard. Farmer (1973) has also reported improvement over 80 days on the Bender-Gestalt and the Graham-Kendall Memory for Designs Test. No controls for practice were used in either of these studies. Long and McLachlan (1974) report an improvement on a number of Halstead-Reitan visual-motor tests, using the previously-mentioned one year delay as a control for practice. However, once again, interpretation of the above results is difficult, since Page and Linden (1974) report improvement on two other visual-motor tasks, the Bender-Gestalt

and Benton Visual Retention Tests, to occur only during the first week after detoxification and not thereafter.

On simpler motor tasks, Tarter and Jones (1971) have reported no changes on the dynamometer and finger oscillation tasks during eight weeks after detoxification, while Goldstein et al. (1968) have reported recovery of gait instability after subjects' cessation of drinking.

Investigations in Our Laboratories — One-Month Recovery Period

To fill these gaps in the research literature, a series of studies was begun in our laboratories in 1974. Particular emphasis was placed on studying the recovery of alcoholics' capacity to learn (modify their behavior based on experience) since this capacity seemed crucial for treatment to be successful. All treatment, after all, is ultimately designed to modify behavior.

The first five studies in the series used an identical design to ascertain recovery parameters for a variety of psychological tasks over a 25-day period. Alcoholic subjects were obtained from the 28-day inpatient alcohol treatment program at Detroit Memorial Hospital. Subjects generally conformed to Jellinek's (1960) "gamma" type alcoholic, and patients with a psychiatric or neurological diagnosis were excluded. In each study, the alcoholic sample was divided into three groups that were equivalent on age, years of education, and drinking history. In some studies, an equivalent non-alcoholic control group, obtained from the general medical wards of Allen Park Veterans Administration Hospital, was included. Group 1 subjects received three administrations of the dependent variable on Days 5, 15, and 25, of the alcohol program. Group 2 subjects only received the Day 15 and 25 administrations, and Group 3 received only the Day 25 administration. Non-alcoholic controls were tested once to provide normal baselines. This design ascertains recovery parameters uncontaminated by practice effects via comparisons between groups across their first testing. Practice effects were discernible by comparisons across groups on Day 25. The combined effects of practice and recovery appeared within the three testings of Group 1.

In the first of these studies (Sharp et al., 1977), we were interested in investigating the recovery of alcoholics' ability to learn novel, meaningful verbal items, since learning meaningful verbal material is requisite for almost any new conceptual task humans undertake. The Synonym Learning Test (SLT) (Kendrick et al., 1965) seemed ideal for this purpose because it incorporated a vocabulary test as a means of equating the difficulty level of verbal items to be learned by each subject. The use of a vocabulary test allowed an assessment of premorbid intelligence, since as was seen in the above review, vocabulary levels have not been found to deteriorate in alcoholics. Once initial vocabulary level was determined, subjects were asked to learn new vocabularies which were beyond their initial capability. This test of new verbal learning had already been shown sensitive to neuropsychological deterioration in an aged population (Kendrick et al., 1965).

The results confirmed that vocabulary level was unimpaired by chronic alcohol abuse, Vocabulary $\bar{x}$, Gp 1 = 25.64, Gp 2 = 27.27, Gp 3 = 24.00, Control = 22.27, whereas the ability to learn new vocabulary words was impaired in the first week after drinking ceased but recovered to normal levels by two weeks post-drinking, SLT $\bar{x}$ adjusted, GP 1 = 55.02, Gp 2 = 74.33, Gp 3 = 76.28, Control = 76.81, F (2, 29) = 3.571, $p < .05$. Interestingly, not only did our alcoholic sample not perform two weeks after drinking as did an aged sample, but no significant relationship was found between test scores and age, $r = .23$, n.s. Nor was length of the alcoholics' drinking history found to affect test scores, $r = .11$, n.s. At least in this sort of verbal test, alcoholics did not perform like an aging population.

In the second study of the series (Ellenberg et al., 1979), we investigated whether similar results would be obtained from a measure of visual-spatial abilities. The use of the verbal and visual-spatial tasks developed by Stark (1961) permitted assessment of visual-spatial paired-associate learning while extending our above findings to a verbal paired-associated task. Since the verbal and visual-spatial Stark tasks had been equated for difficulty levels in normals, any difference found between alcoholics' performance on these two tasks could not be due to one task being inherently more difficult. Furthermore, Stark (1961) developed the test to discriminate between patients with known unilateral brain damage of the left (verbal deficit) or right (visual-spatial deficit) cerebral hemispheres, and Cohen (1968) confirmed that the test discriminated between patients receiving unilateral left or right ECT. Hence, use of the Stark test requires the learning of standard verbal paired-associates, while in the visual-spatial portion, incomplete geometric figures must be completed by the subject.

Results from the verbal portion of the Stark replicated our earlier findings in regard to the learning of novel verbal material in that impairment was present in the first week following the cessation of drinking, but recovery occurred to normal levels by the second week following drinking, Verbal $\bar{x}$, Gp 1 = 26.94, Gp 2 = 14.94, Gp 3 = 17.25, Control = 15.88, F (3,60) = 4.58, $p < .01$. For this verbal task, however, increasing age was related to increasing impairment, $r = .31$, $p < .01$, although drinking history was not, $r = .21$, n.s. In contrast, longer drinking histories combined with greater age did influence visual-spatial recovery, $r_{\text{yrs. alcoholism}} = .46$, $p < .001$, $r_{\text{age}} = .25$, $p < .05$. The majority of alcoholics also showed first-week impairment on this task but similarly recovered to normal levels by the second week after drinking ceased, Visual-Spatial $\bar{x}$, Gp 1 = 27.87, Gp 2 = 18.06, Gp 3 = 25.56, Control = 16.06, F (3,60) = 5.13, $p < .01$. Older subjects with longer drinking histories (more than 12 years), which where over-represented in Group 3 despite efforts to make the groups equivalent, continued to show visual-spatial deficits throughout the 25-day period. Evidently, the claim that alcohol abuse results in greater deficits of right hemisphere functions is not uniformly true. What happens in older, longer drinking alcoholics is not as clear, but may reflect differences in these subjects' ability

to compensate for verbal vs visual-spatial deficits, rather than difference in the organic substrate of these types of abilities (see Ellenberg et al., 1979).

Study 3 (Goldman & Rosenbaum, 1977) of this sequence directly tested the ability of alcoholics to learn information about alcohol abuse that was routinely presented as part of an ongoing treatment program. True-false tests, measuring subjects' retention of the informational content of weekly lectures on the causes, effects, and treatment of alcoholism, were constructed using item analytic procedures. Results showed little improvement from pre-lecture to post-lecture at any of the three time delays following the cessation of drinking. The subjects' learning failures may have been due either to their inability to learn complex material or to a general lack of motivation to learn.

In the three studies reported above, the emphasis was placed on moderately complex forms of verbal and visual-spatial learning. In the two subsequent studies reported below, we turned our attention to basic sensory and motor functioning (Goldman et al., 1978). Measures for these two studies were derived from experimental work in sensory psychophysics and motor learning, so that study findings might be linked to the large existing psychological literature on sensory and motor behavior. Experiment 4 examined cutaneous sensory functioning using standard pressure threshold, two-point threshold, and palmar writing (graphesthesia) techniques. For determination of pressure threshold, subjects were asked to report whether they sensed contact from one of a series of filaments that were differentially graded as to stiffness. For two-point threshold determination, subjects were asked to report whether they sensed the presence of one point or two from a hand-held device which included a caliper for precise adjustment of the distance between two points. In the palmar writing task, subjects were asked to report whether one of the numbers two, three, four, five, or six had been written using an empty pen refill on the subject's palm. All sensory thresholds were determined using the double simultaneous staircase method (Cornsweet, 1962). In this method, the experimenter zeros in on the sensory threshold from both an ascending and descending direction at the same time. That is, the subjects are first presented with a stimulus which is either clearly below threshold or above threshold; with succeeding presentations stimulus intensities are continually brought closer to the subject's threshold. Whether a subject receives a stimulus from the ascending or the descending series on any particular trial is randomly determined. This method precludes determinations that are biased by series effects such as adaptation, preservation, and anticipation.

The findings of this study were as follows: Cutaneous sensitivity to pressure was consistently lower for the alcohol abusers than for controls and did not appear to recover over the entire 25-day period; pressure threshold (in FMG Log 10) $\bar{x}$, Gp 1 = 3.27, Gp 2 = 3.36, Gp 3 = 3.28, Control = 2.16, $F(3, 60) = 5.10$, $p < .01$. In contrast, two-point thresholds of alcoholics were not significantly lower than those of controls at any point during the 25-day recovery;

two-point threshold (in mm) $\bar{x}$, Gp 1 = 5.19, Gp 2 = 6.74, Gp 3 = 6.78, Control = 7.96. Cutaneous form discrimination was considerably more affected during the recovery period immediately after the cessation of drinking; palmar number writing errors $\bar{x}$, Gp 1 = 6.94, Gp 2 = 4.78, Gp 3 = 3.54, Control = 2.78, F (3, 60) = 5.83, $p < .01$. Although considerable recovery occurred over 25 days on this task, performance was not back to normal levels even at the end of the 25-day period, t, (60) = 2.51, $p < .02$. The consistent improvement observed in cutaneous form discrimination over 25 days did, however, suggest that complete recovery might occur over a more extended period. Evidently, while the alcoholics seemed to have lost some skin sensitivity, they retained their ability to process simple sensory information if presented well above threshold. In contrast, the complex perceptual processing demanded by the cutaneous form discrimination task, which presumably requires extensive central integration, appears more vulnerable to alcohol abuse, although potentially recoverable. The skin sensitivity losses observed in this study may be related to the peripheral neuropathy commonly reported in alcohol abusers (Mayer & Garcia-Mullen, 1972). No significant relationship between these tasks and age or drinking history was noted.

In the final study of this series (Goldman et al., 1978), we used a backwards digit writing task to assess the recovery of three motor-learning phenomena, a grooved pegboard to assess the recovery of fine motor coordination, and a hand dynamometer to assess changes in muscle strength. The motor-learning phenomena tested were reminiscence, bilateral transfer, and bilateral transfer of inhibition. Reminiscence refers to the spontaneous increments in motor performance typically observed after rest periods on motor tasks. Bilateral transfer refers to the improvement in task performance by one extremity after practice with a contra-lateral extremity on the identical task. Bilateral transfer of inhibition refers to a decrement in task performance by one extremity that may be observed if rest is not permitted after practise with the contra-lateral extremity. Since bilateral transfer and bilateral transfer of inhibition appear to require efficient communication of information across the cerebral hemispheres via the corpus callosum, it was anticipated that measurement of these phenomena might offer a sensitive method of assessing cerebral function. Results showed that on the bilateral transfer of training task, alcoholics were impaired during the first week of testing but recovered to normal levels by Day 15 after drinking ceased; bilateral transfer $\bar{x}$, Gp 1 = 0.64, Gp 2 = 1.72, Gp 3 = 1.42, Control = 1.79, F (3, 48) = 2.805, $p < .05$. Although both reminiscence and bilateral transfer of inhibition effects appeared to remain below control levels throughout the 25-day period, large intersubject variability precluded significant statistical findings; reminiscence $\bar{x}$, Gp 1 = 0.63, Gp 2 = 0.66, Gp 3 = 0.67, Control = 1.02; bilateral inhibition $\bar{x}$, Gp 1 = 1.22, Gp 2 = 1.30, Gp 3 = 1.66, Control = 1.02. Results on the grooved pegboard showed that alcoholics' fine motor coordination was also impaired during the first week following the cessation of drinking but similarly recovered to normal levels by Day 15 when measured using the non-dominant hand, and tended towards Day 15 recovery when measured using both

hands. Muscle strength, as measured by the hand dynamometer, also significantly improved for both hands by Day 15. Our results with the motor tasks were, therefore, quite similar to those of our first three studies on verbal and visual-spatial new learning, in that deficits present during the first week after drinking ceased showed remarkable recovery by two weeks following drinking. The fact that bilateral transfer also recovered over this relatively short time span suggests that interhemispheric communication via the corpus callosum is not impaired by alcohol abuse. Some significant relationships were found between age and/or years of drinking and first testing scores for the pegboard and dynamometer, but not for the motor learning scores.

When the findings of all five studies are considered in concert, some general recovery patterns may be discerned. First, a number of psychological functions show deficits immediately after drinking ceases, but recover to normal levels by two weeks after drinking. This initial transitory deficit seems to occur mainly in relation to the acquisition of novel behaviors. In contrast, well-practised habits such as retention of vocabulary knowledge appear immune to this transitory deficit. We have previously labeled this acute state of dysfunction the "Zonk" effect (Sharp et al., 1977). The basis for this transitory psychological deficit is as yet unspecified, but may correspond to what Gross et al. (1974) called the acute withdrawal syndrome. These authors suggested that this syndrome might derive from such things as denervation supersensitivity, hypomagnesemia and respiratory alkalosis, and sleep disturbances. To this list we might add psychological distress and lowered motivation deriving from illness and removal of the intoxicant during the first week post-drinking.

Second, tasks that require complex information processing or processing of unfamiliar information such as visual-spatial learning and cutaneo-spatial perception may show more lasting deficits. Though it has been suggested that such deficits may be derived from particular dysfunctions of the right cerebral hemisphere, our data argue that this lateralized damage, if present at all, appears only in older alcoholics with long drinking histories. In fact, it may be possible to explain what appears to be a lateralized deficit on the basis of slower recovery of tasks for which the individual lacks an extensive pre-existing matrix of associations. Verbal items quite likely have such an extensive association matrix related along semantic dimensions.

Finally, tasks primarily dependent on peripheral receptors may show the most permanent deficits, perhaps due to irreversible peripheral organ damage. A recurring deteriorative effect of age and/or years of alcoholism was also noted on many of the tasks. There was also a suggestion that these two variables were related to recoverability of functioning in that older alcoholics with longer drinking histories tended to show more lasting deficits on some tasks.

Recovery of Short-Term Memory in Alcoholics over Eight Weeks after Drinking

We began to extend our investigations of recovery of functioning in alcoholics beyond the one-month recovery period in a study of recovery of short-term memory functioning in alcoholics over eight weeks after they ceased drinking (Vandevusse, 1978). In this study, we used a design identical to that described above except that the three testing points were now one week, four weeks, and eight weeks post-drinking. In order to insure that our alcoholic subjects would remain alcohol-free during our study, we shifted our data-gathering efforts from the previously described one-month inpatient treatment program, to the three-month inpatient program of the Salvation Army Harbor Light Alcoholism Treatment Center in Metropolitan Detroit. Criteria were used for including alcoholic subjects in this study similar to those used in our earlier studies. The subject populations used for the control groups changed, however. In order to make more systematic study of the age variable, we included a college-age group tested at Wayne State University and a group of subjects tested at the Detroit National Guard Armory. Subjects in this latter group were all above the age of 40 years. In this way, we gathered data from two control groups whose different ages would give us indications of changes in test performance due primarily to age. We did lose the advantage of having control groups which were made equivalent to experimental groups by matching procedures. Therefore, any potential group differences due to demographic characteristics other than age were carefully checked and eliminated as sources of variance in test performance.

We chose to study short-term memory in alcoholics because of the critical significance of this subject in Korsakoff's patients. We intended to find out whether alcoholics early in their recovery period show the kinds of serious deficits in short-term memory that Korsakoff's patients typically show. The short-term memory task used in this study conforms to that developed by Peterson and Peterson (1959) with a delay interval of 12 seconds. In the Peterson and Peterson task, subjects first view word triads. They are then asked to perform a distractor task for a brief period of time, after which they are asked to recall the word triads. We chose to use word triads which were linked either along a semantic or an acoustic dimension to determine if these dimensions affected either initial deficits or potential recovery of functioning over the eight-week period. The semantically linked word triads were selected from the lists of animals and weather phenomena included in Battig and Montague (1969). The words in each triad were randomly selected after eliminating words of more than two syllables or words reported by less than 10 of their subjects. The words in the acoustically linked items were based on rhyming words selected from Wood (1943), which had frequency ratings of 10 or above in Kucera and Francis (1969). The stimulus materials were presented on a series of 3 x 5 index cards. The cards were presented by hand at intervals which were timed by an electronic metronome. Subjects were instructed to practise counting backwards from 100 by threes before the institution of the short-term memory task so that backward digit counting could be used as the distractor task. For each triad, a "ready" sign was shown for

three seconds, the word triad was shown for six seconds, a "count" card (at which time, subjects were to count backwards by threes from 100) was presented for 12 seconds and the question mark card was presented for nine seconds. The order of semantically grouped items and acoustically grouped items was counterbalanced among the subjects. Within each item category, the time order was randomly changed between each trial.

For the purpose of data analysis, each of the three alcoholic groups was blocked into two age categories, those subjects under age 35 and those subjects older than age 35. The control groups were included in this analysis as though they were one group blocked into older and younger subdivisions. Table 1 shows the mean number of words recalled in short-term memory broken down into the semantic versus the acoustic items and subdivided along the age blocking. Orders 1 and 2 in this table refer to the different order of presentation of the semantic versus the acoustic items in the counterbalancing procedure. Although there were some difficult to explain effects due to order, it can be seen from Table 1 that for both the semantic and acoustic items the older subjects performed more poorly at the first testing during the first week than did the younger alcoholic subjects or the controls. Although the older subjects clearly improved their performance by the second testing in the fourth week in both the semantic and acoustic items, and continued this improved level of performance through the final testing in the eighth week, they never reached the performance levels of either the younger alcoholics or the control groups. The younger alcoholics, however, also did not improve to control levels by the end of the eighth week. In fact, analysis of variance confirmed these observations in that the older alcoholics were significantly below the performance of the younger alcoholics at all three testing times, $F(3, 63) = 4.69$, $p < .005$. Also, the performance of the older alcoholics in Group 3 (tested at Week 8) was significantly better than the performance of the older subjects in Group 1, with the older subjects in Group 2 falling between their counterparts in Groups 1 and 3. There were no significant differences among the younger alcoholics in Groups 1, 2, and 3, but the younger alcoholics in Group 3 performed significantly worse than controls. It is interesting to note that the learning of semantic versus acoustic items did not differentially affect the recovery curve for the older alcoholics, nor were differentially learned by the younger as compared with the older alcoholics. In sum, while the older alcoholics showed the most severe deficits in short-term memory, the younger alcoholics also showed continuing deficits over an eight-week recovery period. Whether these deficits might recover over a more extended period remains to be seen.

Interaction between Aging and Alcohol

The important linkage between aging and alcoholism observed in our data is of course not new to the psychological literature. The possibility that excessive alcohol consumption causes psychological and biological changes that are similar to those changes normally produced by aging has been suggested by some

TABLE 1: Means of Number of Words Recalled in STM, Broken Down by Age

	TYPES OF ITEMS			
	Semantic[a]		Acoustic[a]	
Group	Younger	Older	Younger	Older
Group 1				
Order 1	14.20	7.67	18.60	7.33
Order 2	13.83	8.00	17.50	14.00
Group 2				
Order 1	7.50	13.00	14.50	11.00
Order 2	16.00	18.50	17.33	9.50
Group 3				
Order 1	15.50	12.00	16.50	13.75
Order 2	16.20	11.50	19.20	12.50
Control				
Order 1	18.00	18.63	20.20	19.64
Order 2	16.86	16.44	19.86	17.67

[a]Summed across eight items

of the earliest research on the effects of alcohol on neurological and neuropsychological functioning (Courville, 1955; Fitzhugh et al., 1965). In such studies, the connection between alcohol and aging has been inferred from the similarity between neuropathological brain changes associated with alcohol use and those produced by aging (Sun et al., 1975), and by indications that some behavioral deficits shown by younger alcoholics are similar to those shown by aging normals (Jones, 1971; Blusewicz et al., 1977; Wilkinson, this volume). Two hypotheses about the interaction between alcohol and aging have been offered. The first is that alcohol accelerates the aging process in a monotonic fashion (Fitzhugh et al., 1965). The second is that the already-aging brain might be more susceptible to alcohol (Goldstein & Shelly, 1971; Jones & Parson, 1971).

The precise nature of the interaction between alcohol and aging has yet to be elucidated in the literature because most studies evaluated this issue as a secondary concern, without thorough contol over the aging factor. Also, the ques-

tion of reversibility was largely ignored, so that some observed deficits in alcoholics which served as a basis for the hypothesized premature aging may, in fact, have been reversible if studied over a time span following drinking. Cermak and Ryback (1977) offered some support for reversibility in a study of short-term memory in younger and older alcoholics.

Neuropsychological Recovery over Three Months

Our most recent undertaking was a study in which we attempted to elaborate our knowledge of the two basic themes that have recurred in our work and that of other investigators. First, we extended our investigation of reversibility of psychological deficit to three months using tasks that are heavily dependent on functions that have shown the slowest recovery in our work; i.e., visual-spatial and sensory-motor functions. Second, we made a deliberate effort to relate all those drinking and demographic characteristics which have been shown to be important in other studies to the three-month recovery parameters.

Our initial problem in designing a three-month recovery study was that our earlier experimental design required additional groups of alcoholics in order to assess any additional data points. Three alcoholic groups were required to assess three recovery points while ruling out improvement due to practice. To study a fourth recovery point, the addition of a fourth alcoholic group would be required; for a fifth data point, a fifth alcoholic group would be required, and so on. The practical limitations of such an approach over a three-month recovery period are obvious. The use of a repeatable neuropsychological test battery designed by Rennick et al. (1972) offered a viable alternative approach. Rennick had selected tests for this battery which were not only quick to administer and had already been shown sensitive to neuropsychological deficit, but were simple enough so that Rennick believed any improvement due strictly to practice would be achieved after only a few administrations of each test. In this way, improvement due to practice would quickly reach asymptotic levels and thereafter further performance increments would reflect actual changes in neuropsychological functioning. This characteristic of the battery had received preliminary confirmation in a study by Rennick et al. (1969) and was further checked in our current study by administration of the tests to two control groups.

To achieve our goal of assessing the effects of a wide range of subject characteristics on recoverability of psychological functioning, we set out to test every admission to the alcohol treatment unit of the Salvation Army Harbor Light Alcoholism Treatment Center in Metropolitan Detroit. The current report includes data collected on 83 inpatient admissions to this program over a two-year period. This sample of subjects reflects a wide range of age, sex, drinking history, and demographic characteristics. Two factors precluded the use of the entire subject sample in all statistical analyses, however. First, as might be expected, there was considerable attrition of patients from the three-month alcohol inpatient program. Obviously, subjects who had left the program could no longer be in-

cluded in our analyses of continuing recovery over an uninterrupted period of three months. Second, although most subjects were admitted to the alcohol treatment program within hours, or at most a few days of their last drink, a number of subjects had been alcohol-free for a longer time than a few days. Data from these subjects also could not be analyzed in the standard way since they did not reflect recovery from the point that drinking ceased. In both cases, however, these factors afforded advantages as well as disadvantages. We found ourselves in a position to study the predictive value of neuropsychological test results on eventual patient dropout from the treatment program, and to study recovery in alcoholics who had been dry longer than three months. Subjects generally met the criteria for Jellinek's (1960) "gamma" type alcoholism, but since the present study was designed in part to examine the effect of a variety of subject variables on test performance, only those subjects with severe psychiatric or neurological impairments were excluded.

Two groups of non-alcoholic control subjects were tested to provide different types of information on baseline test performance. The first control group, 15 Wayne State University undergraduate students, helped determine optimal performance on these tests. No subject in this group consumed more than a few alcoholic drinks per week on the average. The second non-alcoholic control group, 15 male career Army Reserve personnel tested at the Detroit National Guard Armory, provided information on baseline test performance in subjects who were all over the age of 40 years. Since all of these subjects were social drinkers, data could be obtained on neuropsychological test performance based primarily on age effects exclusive of alcoholism effects. Both these groups were also repeatedly tested over a three-month period.

The tests selected from the Rennick Repeatable Cognitive-Perceptual Motor Battery (RCPM) for use in the current study were as follows. (1) The Halstead Finger Tapping test was used to measure motor speed and coordination. (2) The Halstead-Reitan Keyed Pegboard was used to measure visual-motor and tactual-motor speed and coordination. (3) The Digit Symbol Substitution test measured fine visual motor coordination and had some potential for measuring rote learning. (4) The Halstead-Reitan Trail Making Test (Part B) measured subjects' ability to plan, their spatial relations skills, and their immediate working memory. (5) The Digit Span Recall test measured immediate rote memory and concentration. (6) The Color Naming test measured the maximum repetitive performance speed of an elementary language function. (7) The Visual Search test measured visual scanning and visual analyses. (8) The Hand Dynamometer was used to measure muscle strength. Most of these tests are standard neuropsychological tests and will not be explained further herein. The Color Naming test requires subjects to correctly name the colors on sequences of color squares printed on pages of a test booklet. Four different colors are used. The Visual Search test requires subjects to match a small, asymmetrical, checkerboard pattern to the identical pattern which is included within an array of similar patterns printed on a page of a test booklet. All subjects received weekly administrations of the bat-

tery over the three-month time span, except during the first week when three administrations occurred.

Due to the extensive data collected, and the requisite multiple analyses, results are presented in summary fashion with representative data to illustrate salient findings. Curves representing recovery functions for selected subtests of the RCPM battery are presented in Figures 1, 2, and 3. Alcoholic subjects are broken down by age into three groups; those subjects below age 30 (N = 12), those age 30–39 (N = 8), and those age 40 and above (N = 6). The Wayne State and Armory control groups are represented independently on these graphs. It should be remembered that the Armory control group consisted of subjects who were all above the age of 40. It can be seen from these graphs that, although there are some differences among the patterns observed for each subtest, the alcoholics over the age of 40 start the testing sequence with much greater deficits than do the other alcoholics and control groups, and their relative performance deficits are maintained throughout the three-month period. This pattern persists even on such subtests as Visual Search, in which the older alcoholic subjects appear to show some recovery relative to the other alcoholic and control groups, but their deficits in relation to the other groups are still present at the time of final testing. The two younger alcoholic groups show psychological deficits relative to the two control groups early in the testing sequence but then recover relatively quickly to a range that falls generally within normal limits. In fact, when analyses of variance are undertaken using scores of the three alcoholic and two control groups across the first testing, Testing 7, and Testing 14, the continuing dysfunction of the older alcoholics is shown to be statistically significant on the majority of tests throughout the entire test sequence. On those subtests for which statistical significance does not occur, excessive variability of scores appears responsible rather than actual overlap of group means. The two younger alcoholic groups are frequently significantly different from the two control groups at the initial testing but are no longer significantly different by the end of the three-month recovery period. These findings hold even for age-corrected scores on those subtests for which age-corrected norms exist.

Correlational analyses were also undertaken between all the subject characteristics and subjects' performance at their initial testing, using the entire range of alcoholics available to us at the initial testing. This group was obviously larger (N = 83) than the previous subject groups who had completed all 14 testings. Very few subjects were excluded from this analysis because they had not completed even their fourth test battery during the second week of their alcohol treatment program, indicating program drop-out in their first week of the treatment. It was therefore felt that their motivation for performing the tests might be low since they had no intention of remaining through any part of the treatment program.

Since the research in our laboratory reported earlier had consistently revealed the presence of a severe psychological performance deficit in the first

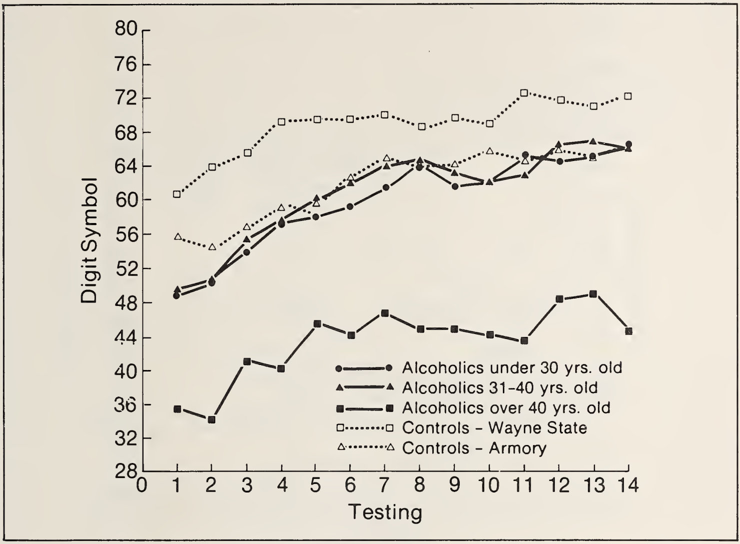

FIGURE 1: *Mean number of digit symbol items completed at each of the 14 testings for the three alcoholic and two control groups. The first three testings occurred during the first week of the alcohol program with the remainder of the testings undertaken on a one per week basis. Armory control subjects were all over 40 years of age.*

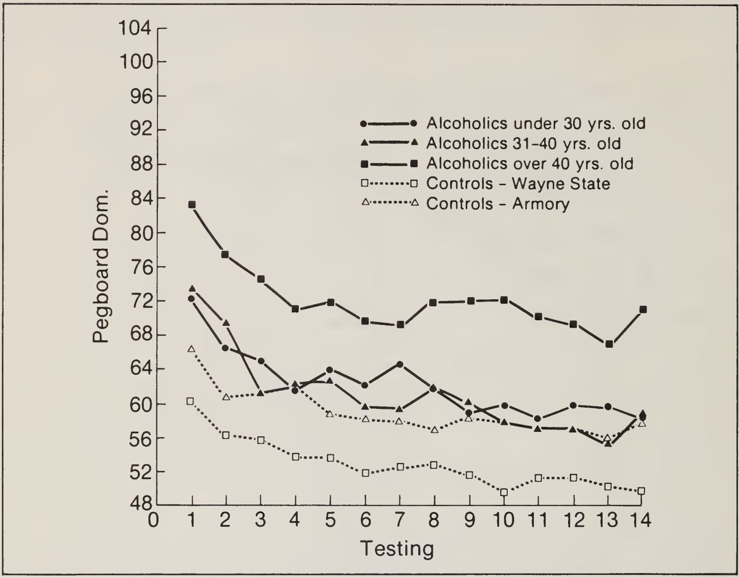

FIGURE 2: *Mean time (in secs) for completion of the grooved pegboard with the subjects dominant hand at each of the 14 testings for the three alcoholic and two control groups. The first three testings occurred during the first week of the alcohol program with the remainder of the testings undertaken on a one per week basis. Armory control subjects were all over 40 years of age.*

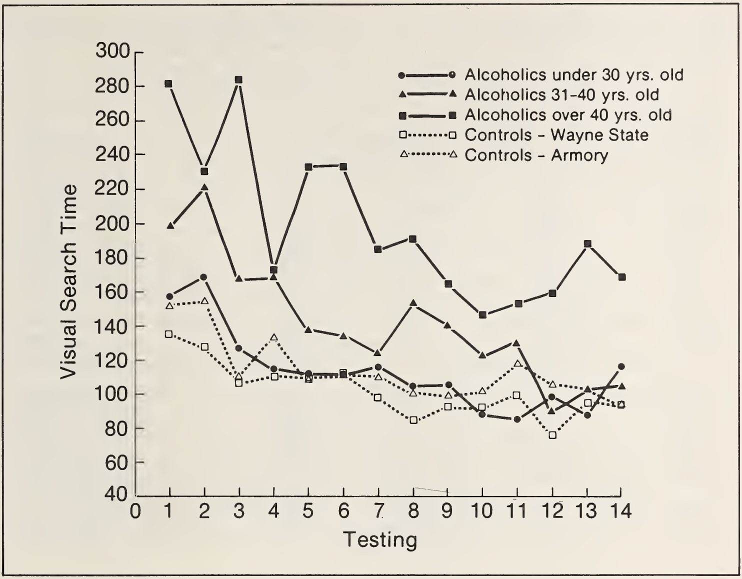

FIGURE 3: *Mean time (in secs) for completion of the visual search task at each of the 14 testings for the three alcoholic and two control groups. The first three testings occurred during the first week of the alcohol program with the remainder of the testings undertaken on a one per week basis. Armory control subjects were all over 40 years of age.*

week after drinking ceased, which often recovered or showed considerable improvement by the second week post-drinking, we broke down our alcoholic samples into two sub-samples for correlation analysis; those alcoholics who received the first test within seven days of their last drink (N = 36) and those who received the first testing beyond seven days of their last drink (N = 47). Correlations between all drinking and demographic variables and initial test performance for those subjects who were tested within seven days of their last drink were generally low and non-significant. The only significant predictors of test performance were age and drinking history. In fact, if age and years of heavy drinking were partialled out, no other significant correlations remained. Thus, the initial test performance for alcoholics who had very recently ceased drinking was quite variable and largely unpredictable from drinking and demographic characteristics. In contrast, many substantial correlations were observed in those subjects tested initially after more than seven days of sobriety. However, once again it was age that was the predominant predictor. Once age was partialled out, most other drinking and demographic characteristics failed to predict initial test performance. Notably, years of drinking, average alcohol consumed per day, and amount consumed at the last drinking episode, did not reliably predict subtest results in this group after age was partialled out. Identical correlational analyses were undertaken with test results collected during the fifth week and twelfth week respectively on all subjects. At the fifth week age became an even stronger predictor of continuing deficits in that age predicted performance on 11 of 12 RCPM measures. A similar pattern continued through Week 12. See Tables 2 and 3 for representative correlations.

In sum, these results showed that alcoholics generally had some deficits in psychological functioning immediately after drinking ceased, although older alcoholics showed greater relative deficits. For alcoholics below the age of 40 years, these performance deficits tended to recover rather quickly as has been seen in our earlier studies. For older alcoholics above the age of 40 years, these deficits showed very little recovery over a three-month time span and were still significantly worse than other alcoholic groups after three months of sobriety. These continuing deficits were clearly not a function of age alone since our Armory control group subjects who were all over the age of 40 years did not show similar deficits. Lasting deficits were evidently a function of both age and excessive use of alcohol. However, it did not seem to matter how much, or in what pattern, alcohol had been used excessively, but rather whether or not excessive alcohol use took place at all. Furthermore, the results appeared to be generally consistent with a critical age hypothesis about the effects of excessive alcohol use, rather than the simple notion that excessive use of alcohol accelerates the aging process in a monotonic fashion. That is, once an individual reaches approximately the age of 40 years, the deleterious effects of excessive alcohol consumption appear to rapidly accentuate neuropsychological deterioration.

Two additional types of analysis were undertaken. First, correlations were computed between subtest scores at the first testing, and the ultimate length of

TABLE 3: Correlations between First Testing Performance, Drinking History, and Age, for Alcoholics Tested More Than Seven Days after Their Last Drink

Variable Partialling	AGE	AGE YRS. DRK.[a]	YRS. DRK.[a]	YRS. DRK.[a] AGE
Digit Symbol	−.73**	−.72**	−.20	.08
Digit Span	−.26	−.26	−.06	.03
Tap-Dominant	−.43*	−.46**	.03	.20
Tap-Non-Dominant	−.52**	−.56**	.00	.22
Visual Search Time	.21	.18	.12	.05
Pegboard Dominant	.64**	.70**	.04	−.36*
Pegboard Non-Dominant	.61**	.65**	.00	−.28
Pegboard Both	.53**	.60**	−.10	−.35*
Color Naming	.22	.21	.07	.00
Trails B	.60**	.63**	.05	−.21
Dynamometer Dominant	−.17	−.24	.15	.22
Dynamometer Non-Dominant	−.14	−.18	.09	.14

[a]Years of Heavy Drinking
*Significant at $p < .05$ level
**Significant at $p < .01$ level

time that the alcoholics remained in the treatment program. To the extent that the length of time alcoholics remained in the program could be taken as a rough index of the success of treatment, it was hoped that neuropsychological test performance early in the treatment program might predict which patients would be most successful in treatment. In fact, except for a few of the subtests which showed moderate correlations, these correlations were generally quite low and non-significant. Apparently, the erratic neuropsychological test performance demonstrated by alcoholics shortly after they stop drinking precludes using such performance as a predictor of ultimate treatment success. Although test scores taken later in the treatment program might be more predictive due to stabilization of test performance, such analyses would obviously be less useful since subjects had already remained in the treatment program for a length of time. In the second analysis, recovery was assessed in those subjects who had been alcohol-free for a substantial time prior to their admission to the alcohol treatment pro-

TABLE 2: Correlations between First Testing Performance, Drinking History, and Age, for Alcoholics Tested within Seven Days of Their Last Drink

Variable Partialling	AGE	AGE YRS. DRK.[a]	YRS. DRK.[a]	YRS. DRK.[a] AGE
Digit Symbol	−.28	−.38	.06	.27
Digit Span	.09	b	.14	.11
Tap-Dominant	.01		.09	.11
Tap-Non-Dominant	−.15		−.05	.05
Visual Search Time	.19		.06	−.06
Pegboard Dominant	.32	.33	.09	−.12
Pegboard Non-Dominant	.25	.38	−.11	−.31
Pegboard Both	.43*	.54**	−.03	−.37
Color Naming	.02		−.06	−.08
Trails B	.32	.42*	−.04	−.29
Dynamometer Dominant	−.13	−.17	.02	.11
Dynamometer Non-Dominant	−.23	−.29	.00	.18

[a]Years of Heavy Drinking
[b]Cells remain empty when extremely low total correlation precludes need for partial correlation
*Significant at $p < .05$ level
**Significant at $p < .01$ level

gram. Such assessment was designed to indicate recovery functions beyond the three-month limitation of the present study. Surprisingly, test performance in the early testings was more impaired than later test performance even for those subjects who had been alcohol-free for a time before testing commenced. This observation will be further addressed subsequently.

Conclusions and Suggestions for Future Work

Except for the rapidly recovering initial deficits observed in all alcoholics on many psychological tests, lasting psychological dysfunction may be primarily confined to older alcoholics on some tasks. These continuing dysfunctions are not merely a consequence of aging, since they are not observed in aging moderate drinkers. Excessive use of alcohol is obviously an important factor in conjunction with aging, although the effects of excessive alcohol use on psychological functioning do not appear to be curvilinear. On some tasks, it does not seem to matter how much an older individual drinks, but only that he/she drinks excessively. The

customary cliché applies to this conclusion, however; more research is obviously warranted. We have yet to establish recovery curves for an extensive range of psychological functions, and we have yet to determine continuous recovery functions for periods longer than three months.

Furthermore, we must determine the exact age at which deteriorative effects due to alcohol begin. The dividing point of 40 years used in our most recent study was arbitrary. The extent of deterioration for more restricted age groups such as 40–45, 46–50, and 51–55 years etc. must be established. We might also attempt to relate deterioration to some independent indicator of aging instead of to an arbitrary number of years.

Clearly, the establishment of psychological recoverability in alcohol abusers requires reevaluation of all conclusions based on studies using one-time assessments. The conclusions of such studies might have been entirely different had the test results been ascertained at a different time delay after drinking ceased. Without the establishment of recovery curves, conclusions cannot be drawn regarding permanent deficits. In future studies, whenever assessment of complete recovery curves is not feasible, care must be taken to assess performance at a consistent time delay after drinking ceases. Conclusions must then be generalized to only that particular delay period.

As indicated by the work of Wilkinson and Carlen (1980), inferences made about cerebral atrophy in alcoholics based on psychological test data are clearly premature. Functional deficits may generally reflect losses in adaptive capacity (new learning) rather than having any direct bearing on brain morphology. Conversely, even if cerebral atrophy were present, the capability for new learning might still allow for apparent recovery on psychological tests. Furthermore, there are indications in our recent data that recovery of some psychological functions may not even begin until individuals are exposed to the particular type of task used to assess deficits. This observation suggests an active type of recovery which requires active practice on the particular task. The notion of active recovery is analogous to a rehabilitation model in which function does not improve without efforts to rehabilitate, even though the deteriorative process may have ceased. An active recovery model contrasts with a passive recovery model, in which improvement occurs merely as a function of the passing of time after the cessation of drinking. Obviously, active recovery is not required for all functional deficits, since the experimental design used in our earlier work demonstrated recovery independent of experience with the task.

Of course, these observations do not preclude the occurrence of actual central nervous system lesions due to chronic alcohol use; such lesions clearly occur and may even be lateralized. They merely suggest that at the behavioral level, both dysfunctions and reversibility of dysfunction may not merely reflect the underlying anatomical substrate. Observed psychological performance may reflect both psychological and neurological processes.

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Reversible Effects of Chronic Alcoholism on the Human Central Nervous System: Possible Biological Mechanisms

Peter L. Carlen

It is becoming increasingly evident that, within certain constraints, the central nervous system (CNS) has significant plasticity (Stein et al., 1974; Cotman, 1978). Previous learning experience can affect CNS morphology, and neuronal morphological alterations may be involved in some processes of learning (Horn et al., 1973). Severe damage to the CNS, whether structural or metabolic, can recover to a large degree in some patients (Ciba symposium, 34, 1975).

Chronic alcohol abuse is associated with cerebral atrophy (Parsons, 1977), neuropsychological deficits (Wechsler, 1941; Wilkinson & Carlen, 1980), and neurological deficits (Victor et al., 1971). Recovery from alcoholic brain damage has been shown functionally and neuropsychologically (Goldstein et al., 1968; Goldman, this volume) and morphologically (Carlen et al., 1978). The present paper summarizes some of the data we have collected, concerning functional and morphological recovery in recently abstinent chronic alcoholics, and includes some speculations about the biological mechanisms responsible for the observed phenomena.

METHODS

Patient Selection

Chronic alcoholics admitted to the Addiction Research Foundation Clinical Institute with at least 10 years' history of drinking more than 80 g of ethanol-day were selected for the study. Patients were categorized clinically by two neurologists. Both impaired and nonimpaired patients were used. Exclusion criteria included: history of head injury requiring hospitalization, clinically evident liver disease (jaundice, hepatomegaly, spider naevi, ascities, persistently abnormal liver function tests), abuse of psychoactive drugs other than alcohol, chronic anticonvulsant or disulfiram use, presence of nonalcohol-related causes of encephalopathy, psychosis, and age greater than 70 years. Psychoactive medication was avoided during patients' hospitalization.

TABLE 1: Weekly Neurological Scores

MENTAL	PHYSICAL
Appearance	Peripheral Neuropathy
Time of Day	Broad Based Gait
Current Date	Tandem Gait
Institution Name	Dysmetria
Institution Address	Resting Tremor
Own Birthdate	Muscle Weakness
Numbers Forward	Nystagmus
Numbers Backward	Ophthalmoplegia
Doctor's Name	Primitive Reflexes
Shopping List	
World War II Dates	SCORING METHOD
Serial Sevens	
Capitals and Presidents	All on scale of 0,1,2, (No, Moderate, or Marked Deficit) except for Nystagmus, Ophthalmoplegia, and Primitive Reflexes which were scored 0 or 1.
Insight	
Confabulation	
Babcock Sentence	

Functional Testing

The following psychological tests were administered in the third week of admission (24.4 ±23.1 (S.D.) days after last drink) and three months later: the Wechsler Adult Intelligence Scale (WAIS) which generates a Verbal Intelligence Quotient (VIQ), a Performance Intelligence Quotient (PIQ), and a Full Scale

Intelligence Quotient (FSIQ); and the Wechsler Memory Scale (MQ). As a possible measure of cerebellar function, a modified form of the Heath Rail test (Heath, 1942) was administered at the time of neuropsychological testing.

A neurological test (DeJong, 1969) was administered, usually at weekly intervals, by a clinical neurologist (Table 1). This examination takes about 10 minutes to perform and there was a high degree of concurrence between different examiners' scores. These tests, which correlate highly with more detailed neuropsychological tests, are routinely used by clinicians to assess encephalopathy and to elucidate neurological signs commonly associated with chronic alcoholism. The correlation coefficients of VIQ, PIQ, and MQ with the Mental score, were −.72, −.65, and −.76 respectively, and with the Physical score, were −.38, −.38, and −.45 respectively.

Computerized Tomographic Scans

Computed tomographic (CT) scans were scored as described by Huckman et al. (1975) with some modifications (Carlen et al., 1978):

V_1 = The difference between the most lateral portion of each of the frontal horns.

V_2 = The intercaudate width of the lateral ventricles.

V_3 = The width of the waist of the lateral ventricles subtracting any clearly visible intervening cerebral tissue, if present.

Sulci = The sum of the width of the eight largest cortical sulci from all CT scan cuts including the Sylvian fissures.

The inter-rater reliability for all the atrophy measurements in 114 scans was $r = .85$ with V_3 having the lowest r of .71 and all other r's > .85.

Repeat CT scans were measured by two observers independently and the two scans of each patient were measured at two different times, not necessarily in sequence.

All scans were done on the EMI Scanner (160 x 160 matrix) at the Toronto General Hospital. Tomographic slices were 8 mm thick.

RESULTS

Neurological Scoring

Using the simple neurological tests scored as per Table 1, functional

improvement was evident during the first six weeks of abstinence in those patients who had their neurological testing starting during the first week of abstinence. Patients' scores ranged from 0 to 38 points. Excluding patients with scores $\leqslant 2$, 15 patients who were tested within two weeks of the last drink and one month later showed the following mean (± S.D.) total scores: one to two weeks, 15.5 ± 7.3; one month later, 9.0 ± 6.8. Practice effect was not controlled.

Psychological Testing

Approximately one-third of all patients showed significant clinically-assessed improvement. Patients improving on one psychological measure did not necessarily improve on other measures. A wide range of difference scores was noted on each of the psychological scores (Figure 1), the greatest changes occurring with the Memory Quotient. On the basis of a clinical history, corroborated when possible, patients were separated into abstinent and non-abstinent groups on their return for retesting, after an interval of 12 weeks. These groups did not differ significantly in mean age or mean test scores. Although there was a tendency for greater mean recovery scores in the abstinent group (Table 2), there was *no* significant difference between the recovery scores of the two groups. These results must be interpreted with caution, since practice effects can greatly influence such results. Recently Catron and Thompson (1979) administered the WAIS to 76 male college students, on two occasions, with various test-retest intervals. For the two-month test-retest group (N = 19) the mean (± SD) change score on the Verbal IQ was 2.27 ± 4.37, and the mean (± SD) change score on the Performance IQ was 8.74 (± 5.95). For the group with a four-month test-retest interval the values were 0.85 (± 5.17) and 8.00 (± 5.42) respectively. When these values are compared with those from Table 2 (where a three-month test-retest interval was used), it appears that the recovery of the alcoholics is principally in performance of the Verbal section of the WAIS.

It is unlikely that the improvement observed was purely the result of practice since there was a negative relationship between the interval from last drink to first psychological test (DLD) and functional change score. This finding is illustrated in Figure 2 for FSIQ of abstinent patients. Although in this example the linear correlation coefficient was statistically significant ($r = -.28$, $p < .05$), in fact, visually, a curve best fits the data points. Similar relationships held for all other functional change scores, including non-abstinent patients, suggesting that in our population the greatest psychological improvement occurred in the first three weeks of abstinence. These data are consistent with controlled studies from other laboratories (see Goldman, this volume).

EEG

In chronic alcoholics, electroencephalographic abnormalities, particularly, slowed alpha frequency, have been shown to improve over the first month of abstinence (Carlen et al., 1977). The change in alpha frequency noted in the first month correlated significantly ($r = .75$, $p < .01$) with the change in MQ

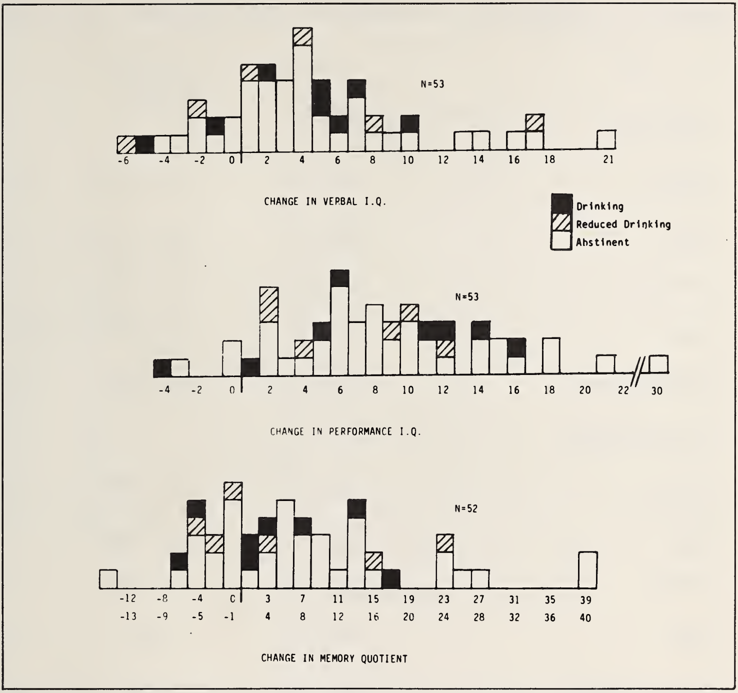

FIGURE 1: *Psychological change scores subtracting the score of the first psychological testing done in the third week of hospitalization from the score of the second psychological testing done three months later. Estimated intertest drinking indicated by empty squares (abstinent), hatched squares (reduced drinking from pre-admission level), and filled squares (usual heavy drinking).*

TABLE 2: Change Scores of Abstinent vs Non-Abstinent Alcoholics

		$\bar{x}$ S.D.	p VALUES (2-Tailed)	N
ABSTINENT				
ΔVIQ	=	4.6 ± 5.6	$p < .001$	39
ΔPIQ	=	8.9 ± 6.4	$p < .001$	39
ΔFSIQ	=	6.8 ± 5.1	$p < .001$	39
ΔMQ	=	8.0 ± 11.9	$p < .001$	38
ΔHEATH RAIL	=	63.2 ± 74.1	$p < .002$	19
NON-ABSTINENT				
ΔVIQ	=	3.6 ± 6.1	$p < .045$	14
ΔPIQ	=	7.1 ± 5.7	$p < .001$	14
ΔFSIQ	=	5.5 ± 4.8	$p < .001$	14
ΔMQ	=	5.0 ± 9.1	N.S.	14
ΔHEATH RAIL	=	23.1 ± 78.3	N.S.	10

measured in 14 patients approximately three weeks and 16 weeks after the last drink (unpublished data).

CSF (Cerebrospinal Fluid) Acidosis

A CSF metabolic acidosis unrelated to systemic acid-base balance was discovered in many of the alcoholics. In some cases this acidosis was measured many weeks after the last drink (Carlen et al., 1980), but tended to decrease with prolonged abstinence. There was a weak but significantly positive correlation between the CSF pH and the DLD ($r = .342$, $p < .01$, $N = 66$). In the first two weeks of abstinence, there were weak but significant correlations between CSF pH values and Neurological Mental Scores. The neurological exams were per-

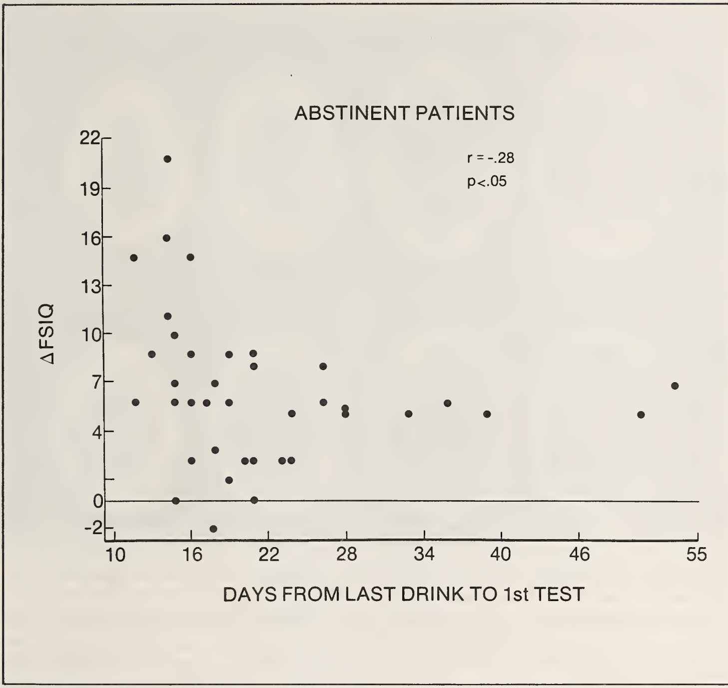

FIGURE 2: *Relationship between change score of FSIQ and time from last drink to administration of first test.*

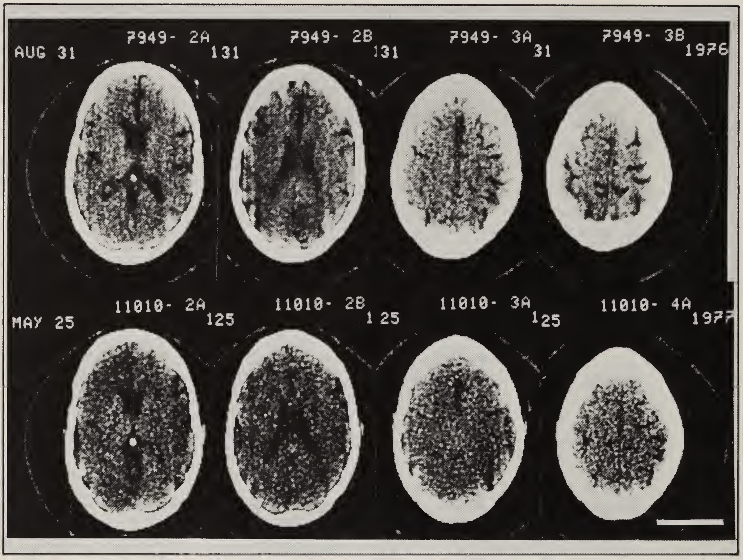

FIGURE 3: *Reversible cerebral atrophy in a recently abstinent 35-year-old male alcoholic who showed a remarkable and steady improvement over 40 weeks of maintained abstinence. Psychological testing, at four and 40 weeks showed a Performance IQ increase of 34 points. Ventricles are dark areas in the central portion of pictures on the left. The typical walnut-shell appearance of cortical and sulcal atrophy is seen in pictures on the right. The top row shows four contiguous CT scan cuts taken four weeks after the patient's last drink and demonstrates enlarged ventricles and numerous and enlarged cortical sulci. The bottom four CT scan cuts taken eight months later show a reduction in ventricular size with a more marked reduction in size and number of visible cortical sulci. Variation in the photographic quality of the two scans cannot account for the observed changes. In a normal patient of the same age, ventricles are much smaller and sulci are usually not visible on CT scans. The calibration line represents 20 mm on standard Polaroid photographs and 7.8 cm in actual tissue. Reproduced with permission from* Science *(Carlen* et al., *1978).*

TABLE 3: Repeat CT Scans

Estimated Interscan Drinking	ABSTINENT	REDUCED DRINKING	DRINKING
N	11	7	5
ΔV_2 (mm)	1.8 ± 2.9*	2.1 ± 4.6	−2.0 ± 1.3
range	6.4 to −3.9	11.2 to −3.9	0 to 3.3
ΔSulci (mm)	5.6 ± 8.8	2.1 ± 10.2	1.5 ± 4.1
range	19.2 to −7.3	16.1 to −10.9	5.96 to −3.3
ΔV_{123}Sulci (mm)	9.9 ± 13.6	5.2 ± 12.7	1.1 ± 10.4
range	29.9 to − 7.3	29.6 to −11.9	14.7 to −9.7
ΔV_{123}Sulci (%)	8.6 ± 12.0	3.2 ± 11.1	1.2 ± 9.4
range	28.8 to −6.9	23.2 to −13.8	13.2 to −9.7
Age	45.0 ± 7.4	45.2 ± 12.4	46.2 ± 10.6

* Mean ± standard deviation. Mean scores are of measurements of the later CT scan minus measurements of the first CT scan in each patient. V_{123} Sulci is the sum of all atrophy measurements. In the abstinent group, only 10 patients were measured for ΔV_2 & ΔV_{123}Sulci.

formed within a week of the lumbar puncture. Neuropsychological scores did not correlate significantly, but many subjects were tested at time intervals greater than one week from time of the lumbar puncture.

Cerebral Atrophy

The most exciting finding in our study was the partially reversible cerebral atrophy noted in some of our subjects who had repeat CT scans (e.g., Figure 3). The results of repeated CT scans in 23 patients are summarized in Table 3. The procedure for scoring the scans has been described elsewhere (Carlen et al., 1978). The scores are the mean of two independent observers' estimations which were highly correlated for scores. The initial V_2 and sulci scores most highly correlated with age and measured functional deficits. The first scan was done within five weeks of the last drink during the patient's hospitalization. The second scan was performed two to nine months later when the patient was no longer in hospital. There was a high degree of variability in the change scores in any one group

(Table 3). Although the mean change scores tended to decrease with increased estimations of interscan drinking, there were no statistically significant differences between the groups using ANOVA analysis (ΔV_2, F = 2.77; Δ Sulci, F = 0.56; ΔV_{123} Sulci, F = 0.86; % change, V_{123} Sulci F = 0.88). The relationship between age and estimated atrophy change showed significant negative correlations in the abstinent group only (Sulci, $r = -.67$, $p < .05$; V_{123}Sulci, $r = -.72$, $p < .02$) suggesting that younger alcoholics have a greater capacity to show decreased cerebral atrophy with maintained abstinence. However, alternative interpretations of this finding are that younger alcoholics drink more heavily or become more malnourished before hospital admission than do older alcoholics, and hence the younger patients have more opportunity for recovery.

DISCUSSION

Chronic alcoholics who cease drinking, at least for the duration of an admission (three to eight weeks) to a treatment facility, demonstrate functional and biological changes which can be interpreted as "improvement." The data presented indicate functional improvement in some alcoholics, including those who resumed drinking after discharge from hospital. The great variance in the functional measurements of change may be partly explained by such factors as variable amount and duration of preadmission alcohol abuse, age, and genetic predisposition. Practice effect must also be considered with improvement on retesting, but other authors controlling for practice effect have also shown functional recovery with repeated neuropsychological testing (Page & Linden, 1974; Clarke & Haughton, 1975; Goldman, this volume).

Biological indices (including CSF acidosis, EEG alpha frequency, and cerebral atrophy) show recovery as well. Correlations between biological and functional measurements rarely predict more than 25% of the covariance (Brewer & Perrett, 1971; Parsons, 1977; Cala et al., 1978; Bergman et al., 1980; Wilkinson & Carlen, 1980). This is probably because both kinds of measurements are poor reflections of the underlying process of alcoholic brain damage and its partial reversibility with abstinence. However, combining biological and functional measures with clinical impression leaves little doubt that marked recovery does occur in some alcoholics.

Although we do not know the underlying biological mechanisms of alcoholic brain damage, enough data are currently available to permit some speculating (Figure 4). Cerebral atrophy is a well known phenomenon in chronic alcoholics, even those not clinically impaired (Brewer & Perrett, 1971; Cala et al., 1978; Lee et al., 1979; Carlen & Wilkinson, 1980; Wilkinson & Carlen, 1980; Carlen et al., 1981). The basis of this atrophy is as yet unclear. In chronically ethanol-treated rats, Riley and Walker (1978) have demonstrated attenuated hippocampal dendrites with decreased spines. If this process occurs throughout the brain of an alcoholic (Carlen et al., 1979), then neurons with decreased processes

for assimilating and transferring electrical-chemical information may provide the basis for functional impairment in chronic alcoholics. The cause of neuronal attenuation may be related to the finding of Noble and Tewari (1973) who showed that chronic ethanol ingestion in mice produced a 50% inhibition of brain protein synthesis. In order to explain the gross cerebral atrophy of alcoholics, one might also invoke concomitantly decreased cerebral support tissue (blood vessels and glia). The CSF acidosis or other biochemical abnormalities may also be important as causes or concomitants of alcoholic brain dysfunction. The duration and amount of ethanol abuse necessary to induce cerebral atrophy in humans is unknown.

Neurons denervated functionally or morphologically tend to atrophy (Horn et al., 1973). It is known that ethanol usually suppresses central neuronal activity (Kalant, 1978). Chronic alcohol abuse could, therefore, indirectly cause neuronal dendritic attenuation by merely chronically decreased neuronal activity throughout the brain. This hypothesis is very difficult if not impossible to test because suppression of neuronal activity *per se* may cause depressed protein synthesis and other biochemical changes, or vice versa (Figure 4).

If chronic alcoholic encephalopathy is a partly reversible CNS metabolic derangement, a certain amount of recovery might be expected with abstinence. To date, it has been presumed that this recovery is due to reversal of biochemical abnormalities such as hypomagnesemia associated with the acute alcoholic withdrawal syndrome (Victor, 1973), or CSF acidosis (Carlen et al., 1980). However, the process of partially reversible cerebral atrophy seen in some recently abstinent alcoholics suggests a cerebral morphological component as well. Certainly the increased CNS protein synthesis seen after alcohol withdrawal in mice supports the hypothesis of regrowth of neuronal processes (Noble & Tewari, 1973) and other cellular elements (Figure 4). Although brain rehydration is a possible explanation for partially reversible cerebral atrophy, preliminary computerized analysis of five repeat CT scans (Penn et al., unpublished observations) shows that the later scans of four abstinent and functionally improved alcoholics with measurably decreased cerebral atrophy had a higher mean cerebral tissue density than the earlier scans. This supports the idea of increased CNS protein rather than lipids (as in myelin) since proteins are denser and lipids are less dense than water.

I do not wish to suggest that neurons are replicating themselves in this situation, but to emphasize that neuronal dendritic trees and axonal arborizations can regrow. It is not unreasonable to expect visually apparent increased cerebral size on CT scan if one hypothesizes that all cortical areas of the brain are affected by the process of alcoholic brain damage and the neuropil regrowth is accompanied by a concomitant regrowth of neuronal support tissues (glia and blood vessels) (Carlen et al., 1979). The fact that in our limited sample, younger abstinent alcoholics tended to show more reversible cerebral atrophy than older

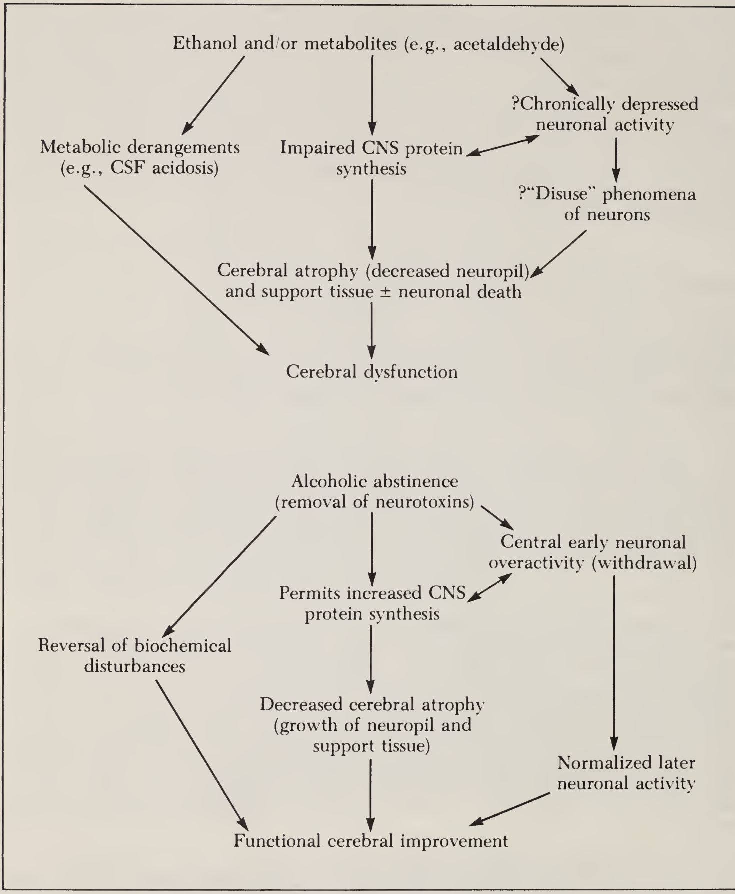

FIGURE 4: *Hypothetical Mechanisms for Development and Recovery of Alcoholic Brain Damage*

abstinent alcoholics goes along with the commonly held view that younger brains have more "plasticity" or more potential for regrowth and remodeling of neuronal processes than older brains. Younger brain-injured patients recover more rapidly and more completely than older patients (Ciba Symposium, 1975).

The fascinating process of functional and biological recovery from alcohol-induced brain damage requires much more clinical and animal research. Many problems remain unresolved, such as: the actual morphologic basis of alcohol-induced cerebral atrophy; the relationship between cerebral morphology (atrophy) and functional deficits; the cellular or biochemical basis of alcoholic brain damage; the relationship (if any) between alcoholic liver disease and brain disease; the relationship between diet, alcohol intake, and brain disease; and the role of genetic predisposition to alcohol-induced impairment.

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An Animal Model of Alcohol-Induced Brain Damage: A Behavioral and Anatomical Analysis

Don W. Walker, Bruce E. Hunter, David E. Barnes, and Joseph N. Riley

A variety of neuropathological (Courville, 1966; Brion, 1969; Victor et al., 1971) and associated neuropsychological (Talland, 1965; Butters & Cermak, 1975; Tarter, 1975; Butters et al., 1977) alterations have been observed in chronic alcoholics. This brain damage and the associated impairment in learning and memory have traditionally been attributed to malnutrition, especially thiamine deficiency (Victor & Adams, 1961), rather than to the direct neurotoxic effects of ethanol. Nevertheless, both neuropathological (Brewer & Perrett, 1971; Freund, 1973; Epstein et al., 1977); and neuropsychological deficits (Jones & Parsons, 1971; Smith et al., 1973) have been observed in alcoholic patients with no history or clinical evidence of malnutrition, head trauma, or exposure to other toxic agents. In human clinical studies it is difficult to achieve a meaningful separation of the possible contribution to measures of function, of the effect of prolonged ethanol exposure *per se* when other variables such as nutrition, environment, aging, heredity, exposure to other toxic agents, or head trauma are uncontrolled. Studies of animals can therefore make valuable contributions toward our understanding of the effects of ethanol *per se* on the structural and functional integrity of the brain, since the necessary experimental control can be more easily obtained, and techniques of investigation can be used that are not available for use in humans.

ACKNOWLEDGEMENTS: This work was supported by the Medical Research Service of the Veterans Administration and NIAAA grants AA00200 and AA03965. We thank Patricia Burnett, Larry Ezell, and Dorothy Robinson for excellent technical assistance.

RESIDUAL BEHAVIORAL DEFICITS AFTER CHRONIC ETHANOL INGESTION IN RODENTS

Failures of Acquisition

Using a nutritionally-controlled rodent model of chronic ethanol exposure, we have previously demonstrated that prolonged ethanol consumption (3–7 months) results in a residual impairment in learning a variety of behavioral tasks including shuttlebox avoidance (Freund & Walker, 1971; Walker & Freund, 1971), temporal discrimination (Walker & Freund 1973), and temporal alternation (Walker & Hunter, 1978). Ethanol was administered in these studies by its incorporation into a nutritionally adequate liquid diet. Control groups received pelleted laboratory food or were pair-fed with the ethanol in the diet. In this paper, we will summarize the results of this series of experiments in which acquisition of several behavioral tasks was studied following chronic exposure of mice and rats to ethanol-containing or control diets (Freund & Walker, 1971; Walker & Freund, 1971, 1973; Walker & Hunter, 1978).

We initially used a shuttle box avoidance task to answer several important questions concerning the functional impairment associated with chronic ethanol consumption in mice (Freund & Walker, 1971): (1) Is the extent of the ethanol-induced learning deficit dependent on the duration of ethanol exposure? (2) Is the behavioral deficit reversible, i.e., does the deficit recover after a prolonged ethanol-free period? (3) Does severe malnutrition result in comparable behavioral deficits?

In order to investigate these questions, ethanol was administered to three-month-old female C57BL/6J mice in the form of a nutritionally adequate liquid diet which contained 35% of its caloric content as ethanol (8.1% v/v). Age-matched control groups were fed either an equivalent liquid diet with isocaloric substitution of sucrose for ethanol (pair-fed to ethanol group) or received free access to pelleted laboratory food. Groups of mice were maintained on these diet regimens for 0, 1.5, 3, 5, or 7 months. Two weeks after the ethanol or sucrose-containing diets were discontinued and changed to laboratory food, the mice were tested in shuttle box avoidance as previously described (Freund & Walker, 1971).

Effects of Chronicity of Administration

Figure 1 illustrates the progressive impairment of shuttle box avoidance learning as the duration of prior ethanol exposure was increased. Note that 3–7 months of chronic ethanol ingestion, but not 1.5 months, resulted in impairment of the subsequently learned shock avoidance task. The rate of acquisition and the asymptotic performance of the laboratory chow and sucrose control groups was statistically indistinguishable.

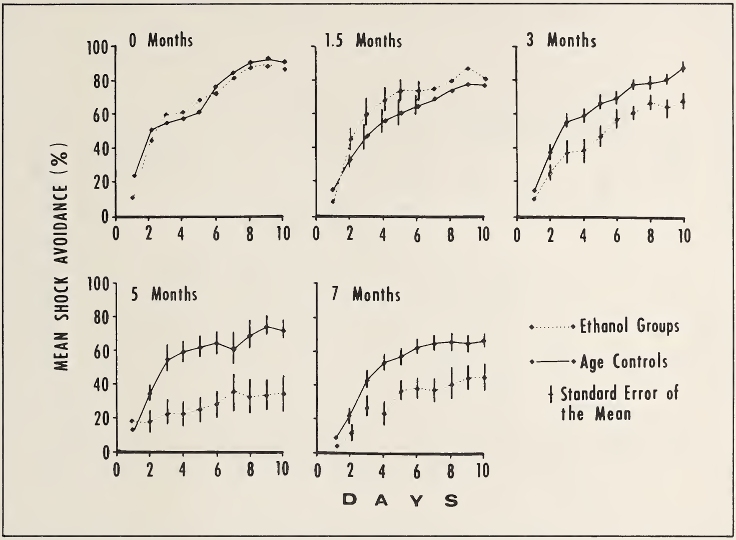

FIGURE 1: *The effect of increasing duration of alcohol consumption on shuttle box avoidance acquisition in mice. Each group was tested two weeks after termination of the ethanol-containing diet in daily sessions consisting of 30 trials each. From Freund and Walker (1971).*

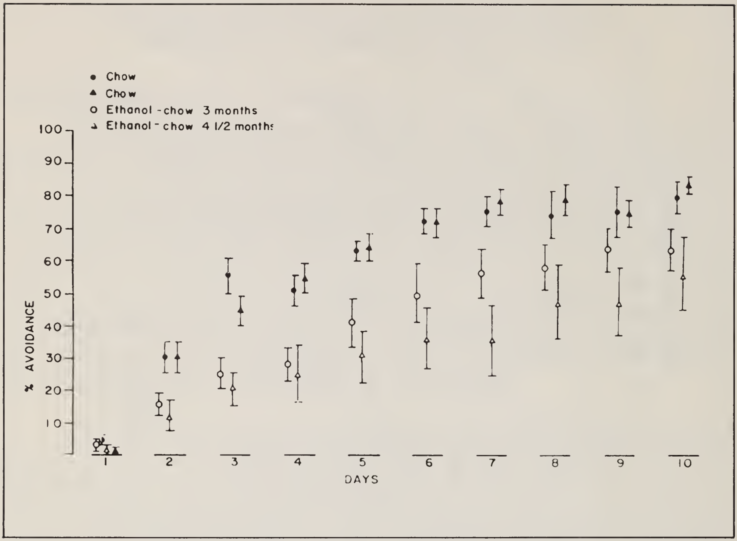

FIGURE 2: *Lack of recovery of impaired shuttle box avoidance acquisition in mice following prior chronic alcohol ingestion. Ethanol diets were fed for five months followed by free access to laboratory chow for 3 or 4.5 months before testing. Age-matched control groups received only laboratory chow during the entire experimental period. From Freund and Walker (1971).*

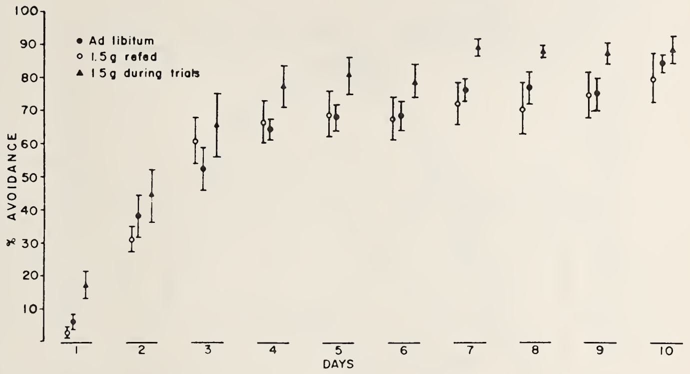

FIGURE 3: *Lack of effect of severe undernutrition on shuttle box avoidance acquisition in mice. Approximately 50% of daily food requirement was fed for three months and continued during testing, or* ad libitum *feeding was reinstated two weeks before testing. Control mice were fed laboratory chow* ad libitum *during the entire experimental period. From Freund and Walker (1971).*

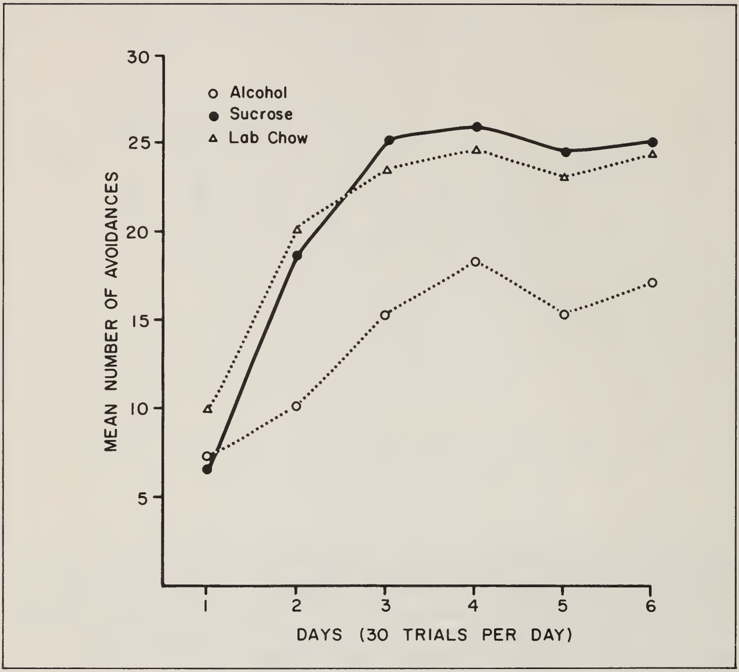

FIGURE 4: *The effect of five months of alcohol consumption on the subsequent acquisition of shuttle box avoidance in rats. Testing was begun two weeks after ethanol exposure was discontinued. From Walker and Freund (1971).*

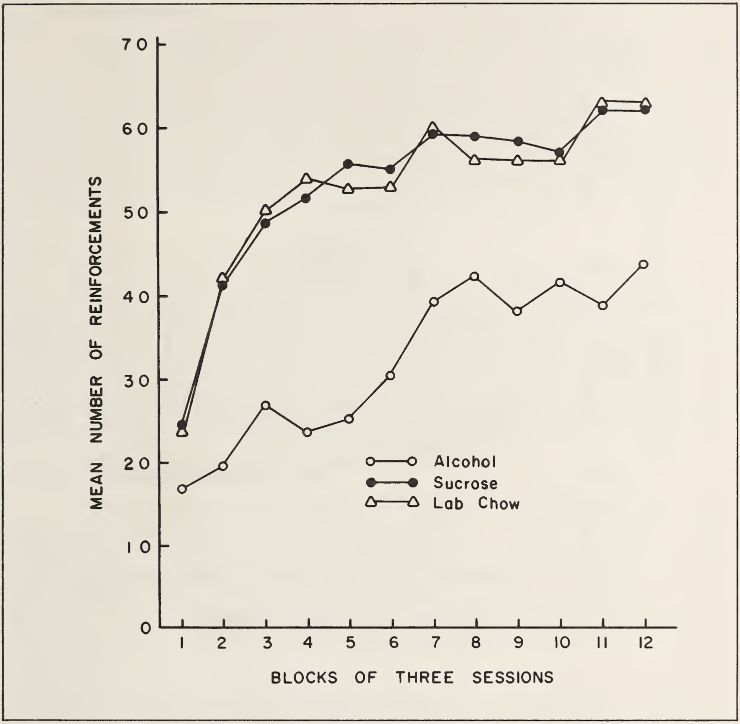

FIGURE 5: *The effect of five months of alcohol consumption on the subsequent acquisition of DRL-20 expressed as mean number of reinforcements earned per session. Training was begun 30 days after ethanol exposure was discontinued and consisted of daily 30 minute testing sessions. From Walker and Freund (1973).*

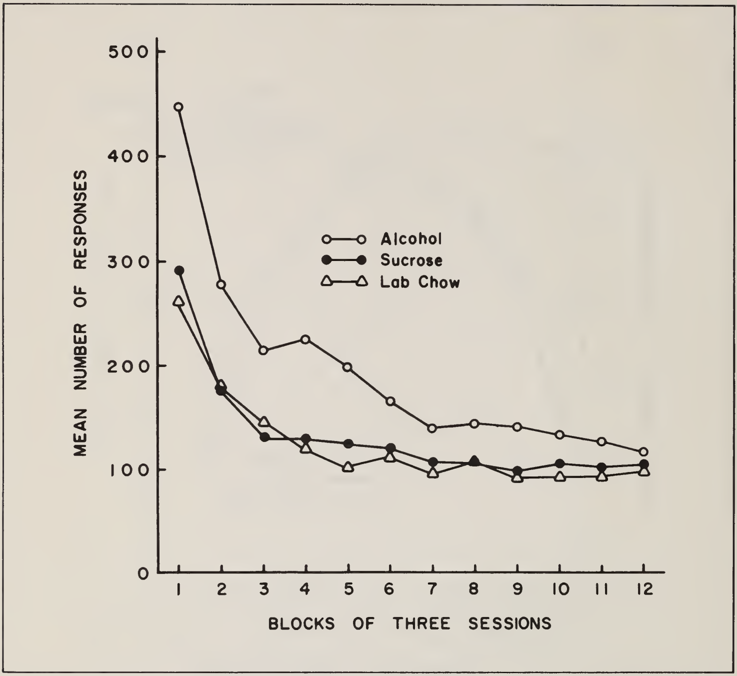

FIGURE 6: *The effect of five months of alcohol consumption on the subsequent acquisition of DRL-20 expressed as the mean number of responses per session. From Walker and Freund (1973).*

Absence of Recovery

In order to determine if the ethanol-induced deficit in shock avoidance recovered with ethanol abstinence the following experiment was done. Three groups of 10 mice each were fed the same ethanol-containing diet for five months. Age-matched control groups received laboratory chow during the entire experimental period. Two weeks, 3 months, and 4.5 months after discontinuation of ethanol, an ethanol and control group were tested for shuttle box acquisition (Figure 2). It is apparent that no recovery from the learning deficit had occurred even after an ethanol-free period of 4.5 months.

Absence of Effects of Malnourishment

It is apparent from the results in Figure 3 that even near-lethal food deprivation for three months does not impair the acquisition of shuttle box learning. In fact, mice in which food deprivation was continued during testing performed slightly better than *ad lib* or refed groups. Therefore, even three months of severe undernutrition did not result in impaired shock avoidance acquisition. A comparable period of ethanol exposure, on the other hand, did result in an enduring behavioral abnormality even under nutritionally-controlled conditions.

Generalization to Rat Model

We next sought to determine if prolonged ethanol ingestion would also result in a shuttle box avoidance deficit in the rat (Walker & Freund, 1971). Adult male Long-Evans hooded rats were maintained on the ethanol or sucrose-containing liquid diets or given free access to laboratory chow for six months. Avoidance training was begun two weeks after the experimental diets were discontinued. As can be seen in Figure 4, six months of chronic ethanol consumption resulted in a severe deficit in the acquisition and asymptotic level of performance.

Generalization to Positively Reinforced Behaviors

In order to determine if the behavioral deficit associated with chronic alcohol consumption was specific to aversively motivated tasks, it was necessary to test the generality of the deficit by investigating the effect of prolonged alcohol consumption on the acquisition of other behavioral tasks. Therefore, we next investigated the effect of chronic ethanol consumption on the acquisition and performance of a differential reinforcement of low rate (DRL) task (Walker & Freund, 1973). Adult male Sprague-Dawley rats were maintained on ethanol-containing or control diets for five months. Thirty days after ethanol exposure was discontinued, the rats were given 36 daily 30-minute sessions of DRL training in which food reinforcement was contingent upon a lever press response following the previous response by 20 seconds or more (DRL-20). Figure 5 illustrates the substantial deficit in DRL acquisition and asymptotic performance by rats previously consuming ethanol for five months. The decreased number of reinforcements received by the alcohol group (Figure 5) was due to poor tem-

poral spacing of responses and not to decreased number of responses as is illustrated by Figure 6.

Studies of Memory

More recently, we sought to determine if chronic alcohol consumption resulted in an impairment of memory processes similar to that reported in chronic alcoholic patients (Butters & Cermak, 1975; Butters et al., 1977). In order to test this hypothesis, rats previously exposed to alcohol for five months, and their controls, were trained in a temporal single-alternation task which we have previously used to examine the memory processes of rats with lesions of the hippocampus (Walker & Means, 1973). After a 60-day alcohol-free period, short-term memory was assessed by training the rats on a discrete-trial temporal-alternation task in which bar presses were reinforced on alternate trials. Performance of the alternation problem was evaluated under conditions of short and long between-trial retention intervals. Although alcohol-treated rats were relatively unimpaired when the retention interval was short, they were severely impaired with the long retention interval. In addition, the performance of alcohol-treated rats was severely disrupted when a distractor task was introduced during the short retention interval. This pattern of results is strikingly similar to that seen in chronic alcoholic and alcoholic Korsakoff patients (Butters & Cermak, 1975; Butters et al., 1977).

Conclusions from Behavioral Studies

It is concluded from the data summarized above that chronic consumption of ethanol *per se*, not malnutrition, results in impairment in brain function as measured by behavioral deficits in a variety of testing paradigms. Behavioral impairment by ethanol consumption is not prevented by large amounts of minerals and vitamins in the diet. The behavioral impairment was shown to increase progressively with the duration of prior ethanol exposure and to endure unabated for a substantial period of time after ethanol treatment was discontinued. Finally, the memory processes of ethanol-treated rats were shown to be sensitive to increases in retention intervals and to interference from distractor activities in a fashion similar to that seen in alcoholic patients. Recently, other laboratories have confirmed our reports of residual ethanol-induced deficits in a variety of behavioral testing paradigms including shuttle box avoidance (Sotzing & Brown, 1976), DRL (MacDonall & Marcucella, 1978; DeNoble & Begleiter, 1979), temporal shock discrimination (Smith et al., 1979), and complex maze learning (Bond & DiGiusto, 1976; Fehr et al., 1976). It seems well-established, then, that prolonged ethanol exposure can result in an enduring alteration in brain function despite good nutrition.

It is likely that the functional impairments observed in alcoholic patients and ethanol-exposed animals are related to specific neuropathological alterations of the central nervous system. Virtually all neuropathological investigations of alcoholic patients have been limited to gross qualitative observations of brain

regions; investigations of more subtle quantitative alterations in nervous system structure have not been reported. Animal studies in which quantitative neurohistological techniques are used to investigate the neurotoxic effect of ethanol on specific populations of neurons should be of significant value in determining the relationship between altered nervous system structure and function associated with alcohol abuse.

NEUROHISTOLOGICAL DEFICITS AFTER CHRONIC ETHANOL INGESTION IN RODENTS

We have recently used quantitative neurohistological techniques to investigate the effect of prolonged ethanol consumption on the structural integrity of the brains of mice (Riley, 1977; Riley & Walker, 1978) and rats (Walker et al., 1980; Barnes et al., unpublished). In this series of experiments, we have found that good nutrition does not protect the brains of ethanol-treated mice or rats from neuropathological alterations. More specifically, we have observed that several months of ethanol consumption results in altered dendritic morphology and a decrease in the number of hippocampal and cerebellar neurons. In the present paper, we wish to summarize the results of this series of experiments. First we will describe the results of our work employing a Golgi analysis to determine the effects of chronic ethanol consumption on the dendritic morphology of hippocampal and cerebellar neurons in the mouse (Riley, 1977; Riley & Walker, 1978). Second, we will describe our more recent experiments in which chronic ethanol consumption in rats results in neuronal loss in the hippocampus and cerebellar vermis.

Altered Dendritic Morphology After Chronic Ethanol Consumption in Mice: A Golgi Analysis

Three groups of mature (90 days old) female mice (C57BL/6J, Jackson Laboratories) were used. One group (group A) received an ethanol-containing liquid diet. A second group (group S) was pair-fed an identical diet, except that sucrose was substituted isocalorically for ethanol. A third group (group LC) received unrestricted access to standard pelleted laboratory food (Lab Chow, Ralston Purina) and water. The liquid diets contained 35% to 42% of the total caloric content as ethanol or sucrose-derived calories. The ethanol containing liquid diet contained 8.1% to 10.3% ethanol (by volume). The percentage of total calories provided by ethanol or sucrose was increased from 35% to 42% in steps of 2% each month. The composition, nutritional adequacy, and procedures for administering the liquid diets have been previously described (Walker & Freund, 1971; Riley & Walker, 1978). After four months' consumption of their respective liquid diets, E and S groups were given unrestricted access to Lab Chow and water for an additional two months before they were sacrificed.

The average daily consumption of ethanol for group A was 24.9 ±1.2 g/kg (mean ±S.E.). This is comparable to the amount of ethanol that has been shown

to result in enduring behavioral deficits in mice (Freund & Walker, 1971). All mice gained weight normally throughout the four-month period of diet administration. There were no statistically significant differences in body weight among the three groups at any point in the experiment.

The brains from five animals from each group were used for histological analysis. After intravascular perfusion with 10% neutral formalin, the brains were removed, coded to prevent experimenter bias, and hemisected by a midline sagittal cut. The material was processed according to a modified Golgi-Kopsch technique developed in our laboratory (Riley, 1979). Sagittal sections of the Golgi-impregnated material were used to analyze quantitatively the dendrites of hippocampal CA1 pyramidal cells, thalamocortical cells of mediodorsal nucleus of the thalamus, and stellate cells in the caudate nucleus. Only neurons that appeared normal and met rigid criteria for adequate impregnation (Chan-Palay & Palay, 1972) were used for quantitative analysis. Dendritic spines were counted on 30μm segments of CA1 pyramidal cell basilar dendrites and dentate granule cell dendrites (Feldman & Dowd, 1975). The dendritic area of Purkinje cells was determined using camera lucida drawings of the maximum extent of Purkinje cell dendritic arborization and converting the area occupied to the unmagnified equivalent in μm^2. The pattern and extent of dendritic branching of thalamocortical neurons in the mediodorsal thalamus was examined according to the method of Sholl (1953). These thalamic neurons do not have dendritic spines.

The number of spines on CA1 pyramidal cells of dentate gyrus granule cells as a function of treatment condition is shown in Figure 7. The number of dendritic spines on pyramidal and granule cells was drastically reduced by 50% to 60% ($p < .001$ in both cases) in the alcohol group relative to controls. The quantitative analysis of the dendritic area of Purkinje cells in the superior cerebellar vermis also demonstrated the deleterious effect of chronic ethanol consumption on these neurons (Figure 8). The average Purkinje cell dendritic area in μm^2 (mean ± S.E.) was 9460 ± 1200 for group A, 12880 ± 1030 for group S, and 13900 ± 710 for group LC. The difference between group A and each of the control groups was statistically significant ($p < .05$). The decrease in the area of Purkinje cell dendritic arborization as a result of chronic ethanol exposure was approximately 25%–30%. On the other hand, no differences among the groups were found in the Sholl analysis of dendritic branching patterns of mediodorsal thalamic cells or in the density of dendritic spines on stellate cells in the striatum.

Qualitative observations of the Golgi material indicated a number of abnormally-appearing hippocampal pyramidal and cerebellar Purkinje neurons. These abnormal-appearing neurons were not used for the quantitative analysis of dendritic spines and dendritic areal measurements. Since the most severely affected neurons were not used for quantitative analysis, the ethanol-induced reduction in the number of dendritic spines on hippocampal pyramidal and dentate granule cells, and the reduced dendritic area of Purkinje cells did not reflect the full extent of the ethanol neurotoxicity observed. In contrast to the observa-

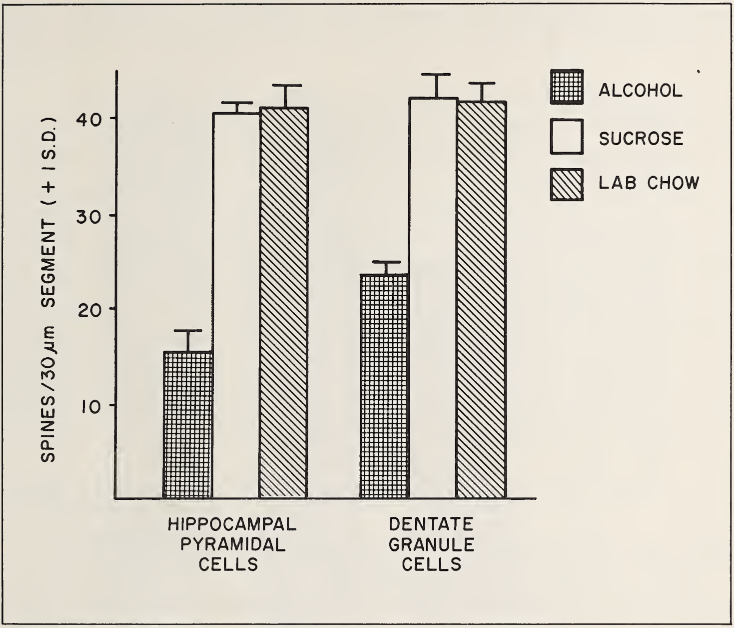

FIGURE 7: *The number of spines per 30-µm dendritic segment of hippocampal (CA1) pyramidal cells and dentate gyrus cells in alcohol-treated and control mice. The values for each group represent the mean of values from five mice. The value for each mouse was the mean of five measurements made on segments of each cell type. Dendritic spines were counted using oil immersion optics. All protrusions from the dendritic shaft, with or without bulbous terminal expansions, were counted as dendritic spines. For CA1 pyramidal cells, the 30µm segment examined was on the caudal-most basilar dendrite beginning 60µm from the closest edge of the cell body. For dentate granule cells, dendrite spines were counted on a 30µm dendritic segment on the caudal-most dendrite located 60µm from the first branching of the primary dendrite. The alcohol group received a nutritionally adequate ethanol-containing liquid diet. The sucrose control group received a sucrose-containing liquid diet (pair-fed to the alcohol group), and the Lab Chow (Ralston Purina Laboratory Chow) control group received pelleted laboratory food and water without restriction. All three groups received their respective treatment diets for four months followed by a two-month period during which all groups were given Lab Chow and water without restriction before sacrifice. From Riley and Walker (1978).*

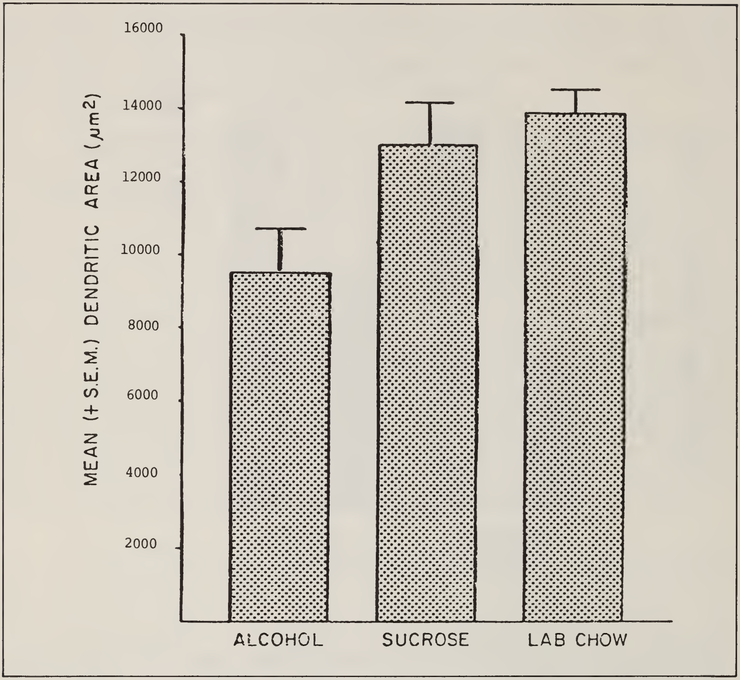

FIGURE 8: *The effect of chronic alcohol consumption in mice on the dendritic area of Golgi-impregnated cerebellar Purkinje cells. The experimental protocol was identical to that described for Figure 7. From Riley and Walker, unpublished.*

tion of qualitatively abnormal hippocampal and cerebellar neurons, no qualitative or quantitative alterations were observed in the mediodorsal thalamus or in the striatum.

Under the conditions of this experiment, chronic alcohol consumption in mice resulted in altered dendritic morphology in neurons of the hippocampal complex and the cerebellar vermis but had no demonstrable effects on neurons in mediodorsal thalamus or the caudate nucleus. This suggests that the hippocampus and cerebellum may be relatively more sensitive to the neurotoxic effects of ethanol than other brain regions. The causal factors involved in the altered dendritic morphology remain to be determined, however. The loss off spines and the dendritic attenuation observed could be due to degenerative processes within the affected neurons (Scheibel et al., 1975) or to transynaptic degeneration due to loss of afferents (Cowan, 1970). The Golgi method did not allow us to determine if the altered dendritic structure we observed was also accompanied by neuronal degeneration that led to a decreased population of neurons. Therefore, in the following experiment we employed quantitative histological techniques that allowed us to determine the effects of chronic ethanol consumption on the population of neurons in the hippocampal complex and the cerebellar vermis.

Neuronal Loss in Hippocampus and Cerebellum After Chronic Ethanol Consumption in Rats

Thirty male Long-Evans hooded rats (Charles River) were used. Rats were individually housed in standard stainless steel cages located in a temperature controlled room with a 12 hr light-dark cycle throughout the experiment. When the rats were 75 days old, they were weighed and divided into three equal, weightmatched groups. One group (group E) received unrestricted access to an ethanol-containing liquid diet. A second group (group S) was pair-fed an identical diet except that sucrose was substituted isocalorically for ethanol. A third group (group LC) received unrestricted access to standard pelleted laboratory food (Lab Chow, Ralston Purina, St. Louis) and tap water throughout the experiment. The liquid diets contained 35% to 39% of the total caloric content as ethanol or sucrose-derived calories. The ethanol containing diet was 8.1% to 9.4% ethanol (by volume). The percentage of total calories provided by ethanol or sucrose was increased from 35% to 39% in steps of 1% each month. The composition, nutritional adequacy, and procedures for administering the liquid diets were identical to those previously described (Walker & Freund, 1971), except Nutrament (Mead Johnson) was used rather than Metrecal. After five months' consumption of their respective liquid diets, E and S groups were given unlimited access to Lab Chow and water for an additional two months before they were sacrificed.

The average daily consumption of ethanol averaged over the five-month period of exposure (mean ±S.E.) for group E was 13.2 ±.33 g/kg. This is comparable to the level of ethanol consumption that results in residual behavioral

deficits in rats (Walker & Freund, 1971, 1973; Walker & Hunter, 1978). There were no statistically significant differences in body weight among the three groups at any point during the experiment. The body weights (mean ±S.E.) at the beginning of liquid diet administration were 245.0 ±4.9 g for group E, 242.0 ± 4.1 g for group S, and 242.0 ± 4.1 g for group LC. The body weights at the end of the five-month experimental diet period were 523.0 ±22.5 g for group E, 517 ±16.8 g for group S, and 497.0 ±10.1 g for group LC.

Two months after the liquid diets were discontinued and all groups changed to Lab Chow, the rats were intracardially perfused with 10% neutral buffered formalin. Brains were removed and coded to allow subsequent analysis without knowledge of group designation. The brains were hemisected by a midline sagittal cut and one-half of each brain was embedded in Paraplast (Sherwood Medical, St. Louis). Sagittal sections were cut at 4 μm-thickness beginning at midline. Every tenth section was saved and mounted for subsequent staining with cresyl violet or hematoxylin and eosin. Anatomically-matched sections from each brain, approximately 1500 μm from midline (Konig & Klippel, 1963), were used for histological analysis of the hippocampus and dentate gyrus. For histological analysis of the cerebellar cortex, anatomically-matched midline sagittal sections through the cerebellar vermis were used. Quantitative determination of the total number of pyramidal cells per section was made by counting at a magnification of 675x each soma containing a clearly defined nucleolus throughout the entire striatum pyramidale from CA1 through CA4 (Lorente de No, 1934). In addition, separate counts were made for the number of pyramidal cells in regions of CA1 and CA2–4. The total number of dentate gyrus granule cells for each section was determined by counting the number of cells in unit areas and multiplying by the total area of the granule cell layer. The number of Purkinje cells having distinct nucleoli were counted in each of the 10 vermal lobules (Larsell, 1952) at 675x. The total number of cerebellar granule cells per section was determined in the granular layer of vermal lobules II, VI, and VIII from density and areal measurements. In addition, the area of the molecular layer in each of vermal lobules II, VI, and VIII was measured in order to determine if the dendritic field of the Purkinje cell layer was altered. After all quantitative and qualitative data were collected for each of the 30 brains, the code was broken and the data assigned to the appropriate group for statistical analysis. Ten brains were quantitatively and qualitatively analyzed for each of the three groups.

The mean number of hippocampal cells per section for each of the three groups is shown in Figure 9. Group means for each CA subdivision were compared by one-factor analyses of variance (ANOVA). In each case, group E was found to have significantly fewer pyramidal cells than groups S and LC: for CA1 ($F = 6.8$, d.f. = 2,27, $p < .005$); for CA2–4 ($F = 8.83$, d.f. = 2,27, $p < .005$); for CA1–4 ($F = 10.2$, d.f. = 2,27, $p < .001$). Group E rats sustained approximately a 16% loss of hippocampal pyramidal cells as a result of five months of ethanol exposure. Table 1 presents the group means for the number of granule cells in the dentate gyrus for the three groups. The total number of granule cells per section

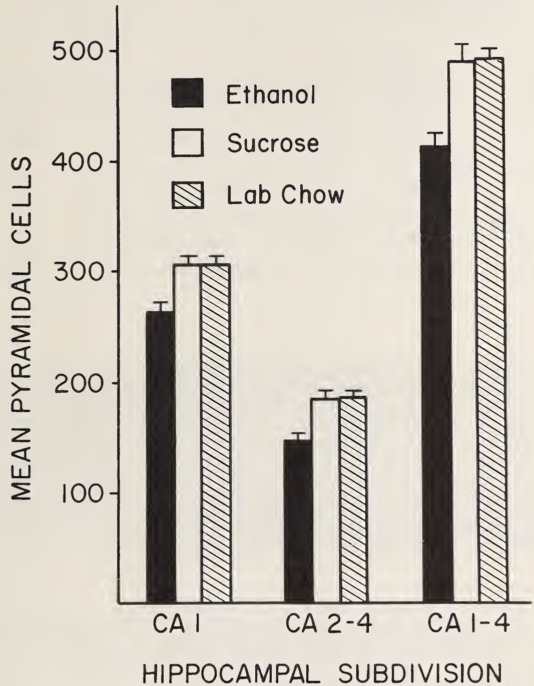

FIGURE 9: *The effect of chronic alcohol consumption on the number of hippocampal pyramidal cells. The values for each group represent the mean (± S.E.) counts for 10 rats. The ethanol-treated group received a nutritionally adequate ethanol-containing liquid diet. The sucrose control group received a sucrose-containing liquid diet (individually pair-fed to the ethanol group), and the Lab Chow (Ralston, Purina) control group received pelleted laboratory food and water without restriction. All groups received their respective diets for five months and then, for a two-month period the rats in all groups were given Lab Chow and water without restriction before they were perfused. From Walker* et al. *(1980).*

TABLE 1: Effect of Chronic Ethanol Consumption on the Morphology of the Granule Cell Layer of the Dentate Gyrus[b]

Treatment Group	AREA OF GRANULE CELL LAYER (mm^2)	GRANULE CELLS per mm^2	GRANULE CELLS per section
Ethanol	.285 ± .017	5664 ± 158	1595 ± 65[a]
Sucrose	.334 ± .024	5987 ± 320	1955 ± 98
Lab Chow	.341 ± .010	5945 ± 220	1995 ± 76

a $p < .005$

b Values are the mean (±S.E.) measurement for each parameter as determined from 10 rats from each group. The measurements were taken from the same histological sections as the data in Figure 9. The cross-sectional area of the granule cell layer was determined by projecting each section onto paper with a projecting microscope, tracing the boundary of the granule cell layer and measuring the area with a compensating polar planimeter. The number of granule cells per mm^2 was determined by determining the average number of granule cells contained within a grid area of .0025 mm^2 at a magnification of 1500x. Six samples of granule cell density were taken in each section, three samples from each of the dorsal and ventral blades of the granule cell layer. The number of granule cells per section was determined for each rat by multiplying the areal and density measurements. From Walker et al. (1980).

reflected by both the reduced area and the density of the granule cell layer, was significantly reduced by approximately 20% in Group E relative to controls (ANOVA, $F = 7.4$, d.f. = 2,27, $p < .005$).

The total number of Purkinje cells per midline sagittal section of the cerebellar vermis was significantly reduced by chronic ethanol ingestion by approximately 15%. The average number of Purkinje cells per section (mean ± S.E.) was 379 ±16.0 for group E, 433 ±15.9 for group S, and 435.3 ±12.1 for group LC. Group E was found to have significantly fewer Purkinje cells ($p < .05$) than either control group. The control groups did not differ from one another. A lobule analysis indicated that lobules V, VI, and VII were the most severely affected, suggesting that chronic ethanol exposure had its greatest effect on the superior vermis. The number of granule cells in the three vermal lobules in which measurements were taken was also significantly reduced by chronic ethanol intake by 20% to 25%. Since the results were similar for each of the three lobules examined, only the data for lobule VI are represented in Table 2. Examination of

TABLE 2: Effects of Chronic Ethanol Consumption on the Morphology of the Molecular and Granule Layer of Lobule VI in Midsagittal Cerebellar Vermis[b]

Treatment Group	AREA OF MOLECULAR LAYER (mm^2)	AREA OF GRANULE LAYER (mm^2)	GRANULE CELLS per mm^2	MEAN TOTAL GRANULE CELLS PER SECTION
Ethanol	[a]1.885 (±.083)	[a]1.144 (±.059)	14.262 (±452)	[a]16.152 (±868)
Sucrose	2.498 (±.161)	1.473 (±.126)	13.420 (±543)	19.503 (±1218)
Lab Chow	2.326 (±.098)	1.352 (±.083)	13.937 (±276)	18.704 (±844)

a $p < .05$

b Values are the mean (± S.E.) measurement for each parameter. The areal and density measurements and the total number of granule cells per 4.0-μm section were determined in the same manner as for the dentate gyrus measurements (Table 1). From Barnes and Walker, unpublished.

Table 2 demonstrates that chronic ethanol consumption decreased both the area occupied by the Purkinje cell layer dendritic field (molecular layer) and the total number of granule cells contained in the granular layer of the midline cerebellar vermis.

In addition to the quantitative changes in hippocampal and cerebellar structure induced by chronic ethanol exposure, we also noted some interesting qualitative abnormalities. During analysis of the coded material, we noticed dark-staining, pyknotic hippocampal pyramidal and cerebellar Purkinje cells. When the code was broken, it was discovered that the majority of the sections containing these abnormally-appearing neurons were from the ethanol-treated group. The appearance of these dark pyknotic neurons was remarkably similar to neurons observed as a result of experimentally-induced ischemia or hypoxia (McGee-Russell et al., 1970; Brown et al., 1979). Darkly-staining, pyknotic neurons in hippocampus have also been observed in monkeys exposed to ethanol by intubation for 16 weeks (Montgomery et al., 1979). When the presence of dark pyknotic neurons is accompanied by significant neuronal loss, as in the present experiment, the dark neurons are thought to be indicative of irreversible cytopathologic damage (Cammermeyer, 1978). We do not want to suggest an interpretation of these qualitative observations at this time, however, since there is not universal agreement on the significance of the dark neuron (Ebels, 1975; Cammermeyer, 1978).

DISCUSSION

It is clear from the present results that five months of chronic ethanol intake results in significant neuronal loss in the rodent hippocampus, dentate gyrus, and cerebellum under nutritionally-controlled conditions. Our previous observations (Riley, 1977; Riley & Walker, 1978) of significant alteration in dendritic morphology in Golgi-impregnated hippocampal and cerebellar neurons in ethanol-treated mice may represent, then, an early phase of a progressive degenerative reaction ultimately ending in neuronal death. These results suggest that previous postmortem reports of histological and histochemical alterations of the hippocampal complex and cerebellum in chronic alcoholic patients (Victor et al., 1959; Martin, 1965; Brion, 1969; McLardy, 1973) may have been a consequence of the direct neurotoxicity of ethanol rather than malnutrition or some other coexisting condition.

The present results also suggest that the neurotoxic effects of ethanol may be regionally specific. Although many other brain regions must yet be quantitatively examined after chronic ethanol exposure, our initial results indicate that chronic ethanol results in structural alterations in the hippocampus and cerebellum without detectable concomitant alteration in the medial thalamus or striatum.

Although the present results demonstrate that prolonged ethanol consumption can have neuropathological consequences despite good nutrition, the mechanism(s) by which it does so remains unclarified. Ethanol (or its metabolite, acetaldehyde) could be directly neurotoxic, or could exert its effect by inhibiting neuronal protein synthesis (Tewari et al., 1978) or by altering cerebral blood flow resulting in chronic ischemia (Goldman et al., 1973). Goldman et al. (1973) reported that acute ethanol intoxication in rats resulted in a reduction in cerebral blood flow specific to the hippocampus and cerebellum suggesting the possibility that chronic ethanol treatment may result in chronic ischemia in these brain regions. Further research will be necessary before the mechanism(s) of action of the neuropathologic consequences of chronic ethanol exposure can be better specified.

It is well known that the hippocampus and cerebellum are particularly susceptible to neuropathological alterations induced by a variety of conditions including anoxia, ischemia, hypoglycemia, various toxic drugs, encephalitis, and aging (Green, 1964; Tomlinson, 1977; Brown et al., 1979). The similarity of the neuropathological and neuropsychological alterations associated with aging and chronic alcoholism in man have led to the hypothesis that chronic alcoholism may accelerate the aging process (Courville, 1966; Blusewicz et al., 1977; Wilkinson, this volume). There is a marked similarity between the histological alterations of the hippocampal complex in rodents induced by aging and the alterations produced by long-term ethanol exposure. Both aging (Geinisman et al., 1978) and long-term ethanol exposure (Riley & Walker, 1978) result in a

reduction of dendritic spines on dentate gyrus granule cells. Hippocampal pyramidal cells are also reduced in number in aged (Landfield et al., 1977; Brizzee & Ordy, 1979) and ethanol-treated rats. The behavioral consequences of aging and chronic ethanol exposure in rodents are also quite similar (Freund & Walker, 1971; Walker & Hunter, 1978; Freund, 1979). It is possible, then, that chronic exposure of the brain to ethanol may accelerate that pathological process associated with biological aging.

The present results, considered together with other reports of morphological alterations of the hippocampal complex associated with prolonged ethanol exposure in mice (Riley & Walker, 1978), non-human primate (Montgomery et al., 1979), and man (Brion, 1969; McLardy, 1973) may also offer some insight into the structural-functional relationship operative in the learning and memory deficits observed in animals (Freund & Walker, 1971; Walker & Freund, 1971, 1973; Bond & DiGusto, 1976; Fehr et al., 1976; Walker & Hunter, 1978; DeNoble & Begleiter, 1979) and man (Talland, 1965; Smith et al., 1973; Butters & Cermak, 1975; Butters et al., 1977) after chronic ethanol exposure. A comparison between the characteristics of the learning and memory deficits of chronic alcoholic and alcoholic Korsakoff patients with hippocampal lesions reveals a marked similarity. Both chronic alcoholic and alcoholic Korsakoff patients (Butters & Cermak, 1975; Butters et al., 1977) and patients with hippocampal lesions (Sidman et al., 1968) are particularly sensitive to increase in retention intervals and interference from distractor activities during short-term memory tasks. Rats with lesions of the hippocampus (Walker & Means, 1973; Winocur, 1979) and rats chronically exposed to ethanol (Walker & Hunter, 1978) are similarly sensitive to increases in retention intervals and intertrial interference. Based on neuropathological studies of alcoholic Korsakoff patients, Victor et al. (1971) have suggested that damage to the dorsomedial thalamus is consistently correlated with impaired memory while Brion (1969) has placed more importance on the mammillary bodies and hippocampus. Future research, in which both quantitative behavioral and neurohistological data are collected in the same set of animals following prolonged ethanol consumption under nutritionally-controlled conditions, should help clarify the relationship between the behavioral and regional neuropathological sequelae of alcohol abuse.

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